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# Testosterone Therapy of Eunuchoids

## II. Clinical comparison of parenteral implantation, and oral administration of testosterone compounds in male eunuchoidism[1]

## [Testosterone in Eunuchoidism]

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As STATED in our first paper of this series (1) entitled, "Implantation of Testosterone Compounds in Cases of Male Eunuchoidism," "the effectiveness of an endocrine preparation is measured best by its capacity to restore normal function in a characteristic endocrinopathy caused by its deficiency. Eunuchoidism, or male hypogonadism, is the clinical state in which the primary deficiency resides in the testes, and therefore it represents an ideal clinical condition for testing the effectiveness of an androgenic substance."

The clinical efficacy of parenteral administration of testosterone propionate in the treatment of male eunuchoidism and of adult forms of male hypogonadism has been confirmed abundantly. For the past three or four years this testosterone preparation has been available in ampules containing 5, 10 and 25 mg. in 1 cc. of oil under the trade names, Perandren (Ciba) Oreton (Schering) and Neo-Hombreol (Roche-Organon).

The effectiveness of implanting pellets of crystalline testosterone compounds, principally methyl testosterone, was reported in our first paper (1). It was demonstrated that in some respects the continuous absorption from such pellets was more efficient and presumably more economical than the injection of the hormone in oil, since only approximately one-fifth of the dose was required to obtain similar results. Furthermore, the improvement achieved by such implants was maintained for about seven weeks, while 2 to 7 injections per week were required to accomplish the same results by the parenteral method.

Since the publication of this paper, we have had the opportunity to determine whether much larger pellets, with consequently greatly augmented dosage, would provide a correspondingly uniform daily absorption so that the interval between implants could be lengthened possibly to several months.[2] Formerly 16 to 23 tiny pellets had been introduced through a large bore needle in doses aggregating from 83 to 195

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[2] As regards this particular phase of the treatment, we wish to express our thanks to the co-author of our first paper, Doctor Gerson R. Biskind.

mg. In the modified procedure a 1-inch incision was necessary and pellets of 200 mg. each were implanted. In each of 2 cases, 4 pellets, totalling 800 mg., were implanted simultaneously.[3] The manufacturers stated that these larger pellets could be more thoroughly sterilized so that possible infection could be avoided. Both methyl testosterone and testosterone propionate pellets were used.

Recently methyl testosterone tablets for oral administration have become available.[4] They are provided in doses of 10 mg. and may be purchased at most pharmacies under the trade names, Metandren (Ciba) Oreton-M (Schering) and Neo-Hombreol (M) (Roche-Organon). Naturally most patients would rather take a few tablets daily than submit to frequent injections over a long period of time. Following the report of Miescher and Tschopp in 1938 (2) that methyl testosterone was effective orally in castrated rats, its successful use in human beings has been reported (3–7). The experience of these authors indicates that from 3 to 6 times the parenteral dose is necessary to produce comparable results orally.

From data collected on our patients treated with testosterone, a fair comparison can be made of the effectiveness, convenience and expense of the oral, the parenteral and the implantation methods. Although we believe that the male hormone has a definite place in the treatment of boys between 14 and 18 years of age who show unmistakable evidence of sexual retardation, this report is restricted to a small group of young men who had reached the age of 21 or over so that the thesis that nature would still mature them could not reasonably be defended. Furthermore, these patients had clinical characteristics of outspoken eunuchoidism (primary hypogonadism) rather than hypophyseal infantilism, dystrophia adiposogenitalis, or Simmonds' disease. In other words, their condition simulated in every respect that found in males who are castrated in childhood, as classically described by von Tandler and Gross many years ago in their study of the Skopec sect in southern Russia. Extreme examples of preadolescent eunuchoidism, although not rare, are by no means common. Therefore our group was necessarily small. A few of the patients included in our previous report were omitted in this paper because they had not been treated by either implantations of the large size pellets or oral administration of methyl testosterone. The 7 patients presented in this report have been observed for a sufficient length of time to be confident of the results obtained. Five of them have been under treatment for 1 to 4 years.

[3] These pellets were furnished by the Ciba Pharmaceutical Products, Inc., Summit, N. J.

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In appraising the improvement or maintenance of improvement in these patients we have been guided by the following data: *a*) subjective observations, *b*) physical findings, and *c*) laboratory 'measuring sticks.' In eunuchoidism the subjective changes noted by the patient, which are either volunteered or ascertained in response to questioning, loom large. In fact, such subjective improvement is of more than ordinary significance and is hardly open to skepticism. The attitude, demeanor and personality of these patients undergo convincing transformations. Moreover, most of them have previously been treated without effect, often for several years, by means of other medications, such as thyroid substance, anterior pituitary-like extracts and the futile orchic substances formerly manufactured. Their elation over the subjective improvement cannot be ascribed to psychic effects produced by the knowledge that they are receiving male hormone.

The subjective changes consist of an increased feeling of well-being, better appetite, development of self-confidence, greater initiative, more energy and endurance, cheerfulness instead of moodiness, and optimism instead of depression. The patient is further encouraged by his ability to obtain a position or promotion in labor or business endeavors. Convincing also is the onset or markedly increased frequency of erections, the appearance of nocturnal emissions, and the desire to masturbate or seek sexual intercourse. Less conspicuous, but occasionally noted, is the disappearance of headaches and indigestion. Rarely, the incidence of convulsive seizures may be diminished.

In the objective sphere the physician can often corroborate the subjective transformation by observing decrease in shyness and increase of manliness, ambition and alertness. Physically the following points are discernible: gain in weight without obesity, which often amounts to as much as 30 lb.; less feminine and more masculine configuration of the body with improved muscular development; more mature features in a patient who, prior to treatment, looked many years younger than his actual age; loss of mammary and mons veneris padding if these were present before treatment; deepening of the voice; appearance, or markedly increased growth, of pubic, axillary and chest hair, or change from a female to a male type of pubic escutcheon; appearance or more vigorous growth of beard or moustache (one of the last evivences of improvement); measurable and photographically demonstrable growth and enlargement of the penis in length and thickness; enlargement and more mature appearance of the scrotum which becomes corrugated and pendulous. The testes, which may have been small or even minute, may enlarge to some extent; on the other hand, their size may not be affected (this is readily understandable since testoster-

one, like thyroid substance in myxedema, does not stimulate the respective gland, but substitutes or supplements for its hormonal deficiency). The previously barely palpable prostate enlarges considerably. Other less conspicuous observations are: a gradual disappearance of the fawn-like pigmentation and fine wrinkling of the skin and a decrease of the reddish-purplish mottling of the extremities. The blood pressure, which sometimes is low, as a rule remains unaffected, but it may rise occasionally.

As regards laboratory procedures, no specific clinically useful test for androgen activity exists that is comparable to blood sugar levels in diabetes and hypoglycemia, calcium-phosphorus values in tetany and osteitis fibrosa cystica, the B.M.R. as a measure of thyroid function, or the electrolyte pattern in Addison's disease. The creatin excretion is often disturbed, although we have not studied this reaction consistently in our patients. Likewise, there may be some change in the blood plasma cholesterol which, however, is not unique. In some cases the B.M.R. is decidedly below normal. It may become normal under testosterone therapy without the addition of thyroid substance. Kearns (5) in an effort "to obtain objective measurements to supplement the oft repeated subjective record of the patient pertaining to increased endurance," utilized "six tests for performance in exercise and in staying power." Definite improvement was thus objectively ascertainable. We have not carried out similar tests. Also androgen excretion assays have been abandoned in our studies. In all cases the amount of androgen was diminished or absent before treatment, and occasionally it increased upon testosterone therapy. However, the use of this test does not seem warranted in clinical practice because of its limited usefulness and the elaborate, time-consuming and expensive laboratory procedure necessary for accurate determinations. Eunuchoidism originating in childhood almost always is associated with an appreciable delay in epiphyseal union and the resulting retardation in bone age. Concomitant with the development of sexual maturity by testosterone therapy, epiphyseal fusion may be accelerated. However, determination of this fact also is not necessary as a check on treatment.

Herewith follow terse summaries of the 7 cases in our series. Five of these have been reported previously in more elaborate detail with photographs (1); they are included here because, as has been stated, additional information has been accumulated regarding various methods of administering testosterone compounds. Since the patients have been observed for long periods of time, these records are especially valuable and permit enlightening comparisons of oral, parenteral and implantation therapy.

*Case 1.* R. C. (*U57397*) (*Case 7* in previous paper) (fig. 1-A, B, C, D, E, and F). The patient was 24 years old when he was first seen in April 1940, with characteristic preadolescent eunuchoidism. His height was 66¾ in. and his weight 120 lb. He had typical disproportionately long extremities, shaved infrequently and had a high-pitched voice. His pubic hair was scant and axillary growth was moderate. The penis was small (length 5 cm.) and the testes were the size of small olive pits. The left testis was undescended. The prostate was barely palpable. His bone age was 16 to 17 (at 24 years of age).

Implants of methyl testosterone were begun on April 17, 1940. During the following 8 months 4 implants of tiny pellets were introduced subcutaneously through a large bore needle; the dose varied from 143 to 180 mg. Marked subjective and objective improvement resulted. Priapism persisted for one week following the first implant. The stimulating effects lasted from 4½ to 7 weeks after each implantation during which time the patient had frequent erections and some nocturnal emissions; he masturbated occasionally. The length of the penis had increased to 8 cm.; its circumference was 8 cm. Scrotum and testes increased in size; the left testis had descended shortly after the first implant. The patient gained 13 lb. and felt stronger. His voice deepened, his body hair increased and he shaved every week.

In December 1940, 4 pellets of methyl testosterone totalling 800 mg. were implanted through a small incision in the back. The patient noticed unmistakable effects within a few days. During the first week he had 3 to 4 erections daily and 2 nocturnal emissions. His voice deepened somewhat, his beard became heavier and his penis increased ¾ cm. in length. Two months later the muscles of his arms and legs had developed noticeably and his general strength had improved. He reported 5 to 6 erections daily, 3 nocturnal emissions a week and greater attraction toward the opposite sex. The size of his genitalia was unaltered. He had gained 3¼ lb.; the total gain in weight under implantation therapy was 16¼ lb. He had not received any other treatment, so that this gain was directly attributable to the implantations of male hormone.

Two months later (4 months after the implantation of 800 mg.), the stimulating effects had, in the patient's words, "run out." Until 2 weeks before, he had had 3 to 4 erections a day, but since that time they had diminished to one a day or none at all. Whereas he had previously had one to two nocturnal emissions a week, he had had only one in the previous 2 weeks. The size of the penis and testes had not changed significantly as a result of this implant. The prostate, which was barely palpable at the beginning of treatment, was considered two-thirds of normal size a year later.

In this patient, the only benefit derived from the implantation of an amount of testosterone 4 to 5 times greater than the implants of smaller pellets was an increased duration of effect which was not, however, in proportion to the size of the dose. The subjective and objective benefits were maintained satisfactorily for a period of 3½ months. At the end of this period, when the effect of the deposit of testosterone was exhausted, some soreness developed at the site of the implant. When the incision was

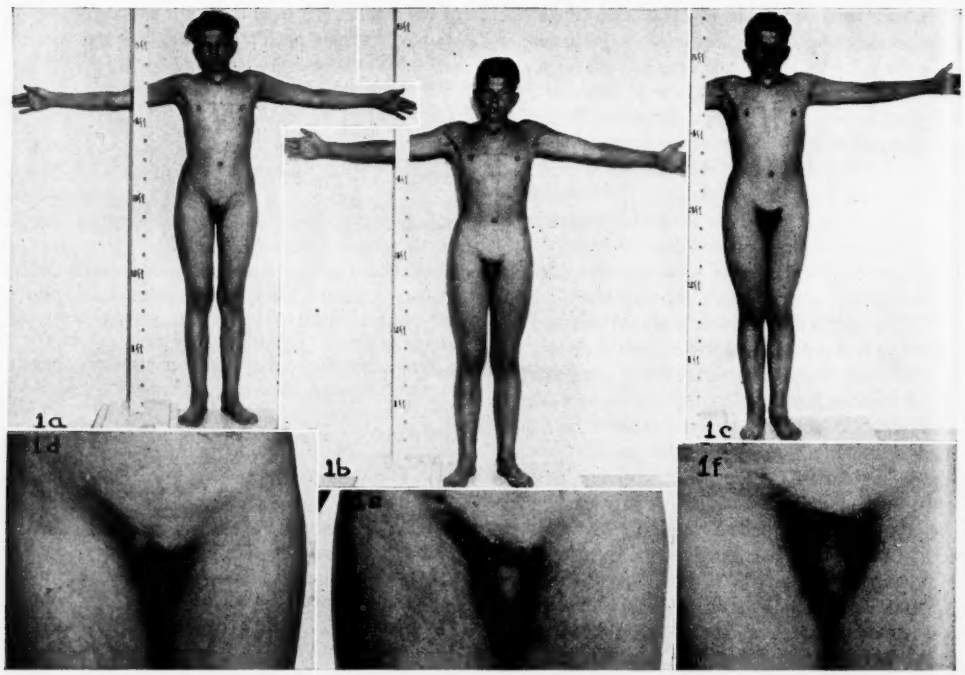


Fig. 1. PREADOLESCENT EUNUCHOIDISM. *Case 1. R. C.* age 24 yrs., a and d, April 1940; b and e, August 1940; c and f, April 1941; April 1940 to Sept. 1940, 4 implants of 180, 147, 158 and 143 mg. each of methyl testosterone; a 5th implant of 800 mg. in Dec. 1940.

reopened, a small sterile abscess was encountered together with 4 pellets which were one-third to one-half their original size. After drying they weighed 370 mg. The fibrous tissue reaction which had developed around the whole area, apparently had interfered with the complete absorption of the pellets. During the one year of testosterone implantation therapy, the patient had grown one inch although he was 24 years old when treatment was begun. A check of his bone age failed to show any convincing change.

*Case 2. A. H. (U39262)* (*Case 5* in previous paper, with photographs). This typical preadolescent eunuchoid was 26 years old when he was first seen in May 1934. He was 70½ in. tall, weighed 118 lb. and had characteristically long extremities. He shaved every 2 weeks, had sparse axillary hair, moderate pubic hair and a tiny penis (length 2½ cm.) with the circumference of a lead pencil. The scrotum was very small and contained testes the size of date seeds. Basal metabolic rate was −18%. Bone age was 14 years (at 26 years of age). Previous endocrine therapy had been futile.

Parenteral administration of testosterone propionate was begun in March 1939, in doses of 25 mg. 3 times a week for 3 months (a total dose of 1,250 mg.). The patient had continuous priapism during the first week of treatment and frequent erections thereafter. The frequency and severity of migraine attacks were somewhat diminished and the patient gained 15 lb. Other effects were more vigorous growth of beard, increase in size of the penis to 3¾ cm. and slight increase in the size of the testes. The B.M.R. remained −17%.

During the next 2 months the injections of 25 mg. 3 times weekly were continued, and in addition inunctions of testosterone propionate ointment (4 mg.) were applied nightly. As a result the length of the penis increased to 4½ cm.

Testosterone propionate injections 3 times a week were then continued for 11 months until February 1940. At this time the patient had frequent erections and emissions, his voice had deepened and his beard and body hair had grown heavier. The penis had grown to 6 cm. in length, B.M.R. was −2% and his weight was 151 lb. (a gain of 18 lb.).

During the next 9 months, in addition to the injections of 25 mg. 3 times weekly, he received 6 implants of tiny pellets administered subcutaneously through a large bore needle. The dose per implant varied from 100.7 mg. to 195.3 mg. of methyl testosterone. Further sexual stimulation resulted and the penis increased to 7¼ cm. in length.

At this time the patient had to move across the continent because of his business. He was given a single implant of 800 mg. in 4 large tablets which were placed in the subcutaneous tissues of the back through a small incision. The parenteral therapy was discontinued. Two months later the patient reported definite stimulation which was, however, not as great as that experienced with the combination of injections and implants.

Aside from the longer duration of effect from the one

large implant, no advantages have been apparent. Since the patient is now 3000 miles away, further follow-up is difficult. He represents the most severe case of uncastrated hypogonadism that we have encountered and his requirements from now on will entail a heavy financial outlay. To maintain or augment the improvement achieved, frequent injections of testosterone propionate and oral administration of methyl testosterone are required. An adequate amount of the preparations obtained through the usual channels at present prices would cost the patient at least $50 a month.

*Case* 3. *L. K.* (*U20634*) (*Case* 3 in previous paper) (fig. 2-A, B, C, D, E, F, and G). The patient was 24 years old when he was first seen in September 1937. He had been operated upon for bilateral cryptorchidism at the age of 16; at that time the left testicle had been atrophic. His height was 71¾ in., his weight 146 lb. He had the disproportionately long arms and legs of a typical eunuchoid. He had never shaved and his voice was high-pitched. Pubic hair was sparse and only a very few axillary hairs were present. The penis was small (length 4¾ cm.) and the scrotal content consisted of some questionable tissue in the left side. His bone age was 15 (at 24 years of age). Equine gonadotropic hormone had been administered (48 injections in 4 months) without benefit.

Testosterone propionate was given parenterally for 16 months; the total amount was 3,500 mg. Thereupon his voice deepened and occasional nocturnal emissions and masturbation occurred. The hair in the pubic escutcheon increased moderately and the axillary hair grew considerably. The length of the penis was 8 cm. (formerly 4¾ cm.) and the circumference was 10 cm. The testes were palpable; the right was bean sized and the left was the size of a small olive. The bone age was 19 years (an acceleration of 4 years in 2 years' elapsed time). Increased mental and emotional responses as well as vigor and strength were evident. He had gained 20 lb.

In the following year (November 1939 to November 1940) the patient received 5 implants of methyl testosterone introduced subcutaneously through a large bore needle. The dosage, given in tiny pellets, varied from 101.3 mg. to 164 mg. The improvement obtained by the parenteral method was maintained both subjectively and objectively. Libido remained unchanged for as long as 9 weeks. During this period the patient married and was able to have successful intercourse as often as once a week.

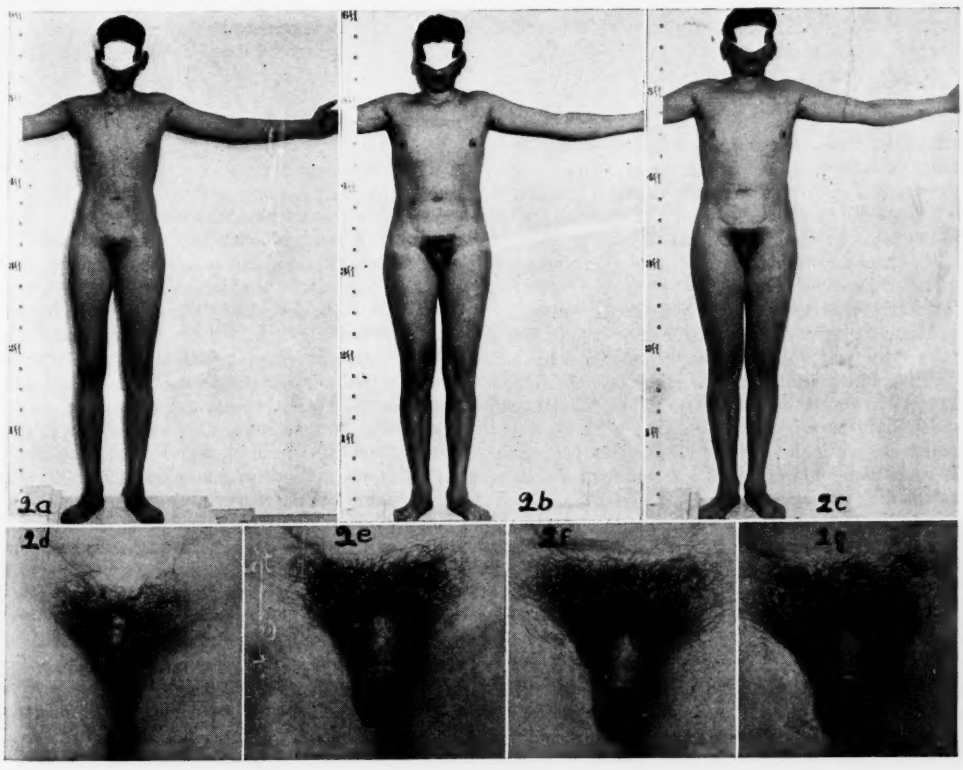


Fig. 2. PREADOLESCENT EUNUCHOIDISM. *Case* 3. *L. K.* age 25 yrs., a and d, April 7, 1938; e, Nov. 15, 1939; b and f, Nov. 7, 1940; c and g, March 27, 1941; April 7, 1938 to Nov. 15, 1939 injections of 25 mg. methyl testosterone 3 times per week; Nov. 15, 1939 to Nov. 7, 1940, five implantations of methyl testosterone totaling 651 mg.; Nov. 7, 1940 to March 27, 1941, 10 mg. methyl testosterone 3 times daily.

The length of the penis increased further 2 cm. and the patient now shaved once a week.

In November 1940, when the patient was 27 years old, oral therapy was instituted. For the first 4 months he received one 10 mg. tablet of methyl testosterone 3 times daily. The effect of the implant given 2 months before had begun to wane so that he had not had intercourse during the month prior to institution of oral therapy. The tablets stimulated him almost immediately; 2 days later he had erections 3 times a day and he reported successful intercourse 3 times in the subsequent month.

Four months after the beginning of oral therapy, the dose was reduced from 30 to 20 mg. daily to determine whether this diminished amount would suffice. A month later the patient reported that within 2 weeks of reducing the dose, the frequency of erections had diminished somewhat. However his libido had remained the same. It seemed doubtful that a dose of 20 mg. daily by mouth would continue to be adequate for this patient. It was therefore again increased to 30 mg. daily. Evidently, then oral administration of 210 mg. a week has in this patient an effect equivalent to parenteral administration of 75 mg. a week. This is a ratio of not quite three to one.

*Case 4. J. J.* (*U36521*) *Case 4* in previous paper, with photographs). The patient was 31 years old when he was first seen in May 1938. He gave a history of epileptiform seizures from the age of 16, but he had had none in the preceding 2 years. He had typical preadolescent eunuchoidism with disproportionately long extremities. His height was 71 in., his weight 123 lb. His voice was high-pitched; he had a few axillary hairs and a moderate amount of pubic hair. He clipped the fuzz from his face every two or three weeks. His penis was small (length 4½ cm.). Testes and scrotum were very small; the prostate was not palpable. The bone age was 18 years (at 31 years of age). He had been given equine gonadotropic hormone for 3 months without effect.

Parenteral administration of testesterone propionate was begun in January 1939 in doses of 25 mg. 3 times a week for one year; the total dose was 3800 mg. Marked subjective and objective improvement resulted. He had frequent erections and practiced occasional masturbation and sexual intercourse. Other effects were increased strength and a gain in weight of 14½ lb. The penis grew 3½ cm. so that it now measured 8 cm. in length. The prostate enlarged to one-half normal size. The bone age advanced slightly.

In February 1940 implantation therapy was begun. During the succeeding 9 months the patient received 4 implants of methyl testosterone varying in size from 102.7 to 148.1 mg. The previous benefits were maintained and the stimulation from each implant lasted from 7 to 15 weeks. Libido and potency remained about the same and the penis grew slightly larger, to 9 cm. in length.

In November 1940, oral therapy of methyl testosterone, 10 mg. 3 times daily, was instituted. Sexual stimulation was prompt; it was noticeable in 48 hours. The patient had successful intercourse twice in the following 2 weeks and erections 2 and 3 times daily. The penis grew 1¾ cm. in length and 1¼ cm. in circumference in these 2 weeks. On April 3, 1941, 5 months after beginning of oral therapy, the patient had gained 6 lb. and had felt increase in strength. His bone age had advanced to between 19 and 22 years of age. The subjective benefits previously obtained from parenteral and implantation therapy were well maintained on a dose of 30 mg. daily by mouth. No further significant change occurred in the size of the genitalia and the secondary sexual characteristics were about the same as when oral therapy was begun. The size of the prostate had not changed during the previous 8 months.

*Case 5. B. C.* (*U4545*) (*Case 6* in previous paper, with photographs). The patient was 17 years old when he was first seen in March 1933. He showed characteristic evidence of preadolescent eunuchoidism with disproportionately long extremities. His height was 63¾ in. and his weight 114 lb. His voice was high-pitched and he had no beard, axillary nor pubic hair. The penis was small (7 cm. in length) and the testes were the size of small olives. The prostate was barely palpable. The bone age was 15 to 17 years (at 17 years). The B.M.R. was −24%. Treatment with Antuitrin-S, thyroid substance and androstine had had negligible effect.

In November 1936, when the patient was 21 years of age, treatment with testosterone propionate was begun. At first 5 mg. and later 25 mg. were given 3 times each week parenterally. This plan was continued for a period of 3 years, until November 1939. The total dose was 10,250 mg. Marked changes occurred during this time. The patient matured markedly, shaved every 2 weeks, had a moderate growth of axillary and pubic hair, and his penis had adult dimensions. Treatment then had to be discontinued for 4 months with consequent subjective and objective regression of noticeable degree. The penis shrunk 2 cm. in length.

In March 1940, implantation therapy was instituted. During the following 8 months the patient received 3 implants varying in dosage from 109.6 to 138.3 mg. Sexual stimulation and an increase in general strength returned. The patient's weight remained constant, but his penis again increased in length, from 9¼ cm. to 12 cm.

Oral therapy was begun in November 1940 with 10 mg. of methyl testosterone 3 times daily. This resulted in such marked sexual stimulation that on December 19, 1940, the dose was cut to 10 mg. twice daily and in February it was further reduced to 10 mg. daily. Two months later the patient expressed his entire satisfaction with the effects of this dose. His general strength had improved and he had gained 10 lb. during the period of oral treatment. He shaved once or twice a week. Erections occurred one to two times daily. He masturbated twice a week and experienced an occasional nocturnal emission. The external genitalia were slightly larger and of full adult size. In contrast, the prostate remained small and soft, about one-fourth normal size.

The patient stated that he preferred oral to parenteral treatment, principally because it was convenient. He also preferred oral therapy to implantations because the tablets provided a more uniform stimulus whereas the implants "built up to a peak and then let down."

*Case 6. F. V.* (*U62077*) (not previously reported) (fig. 3-A, B, C, D, E, F, and G). This 24-year-old sandblast helper was first seen as a private patient in July 1940. His

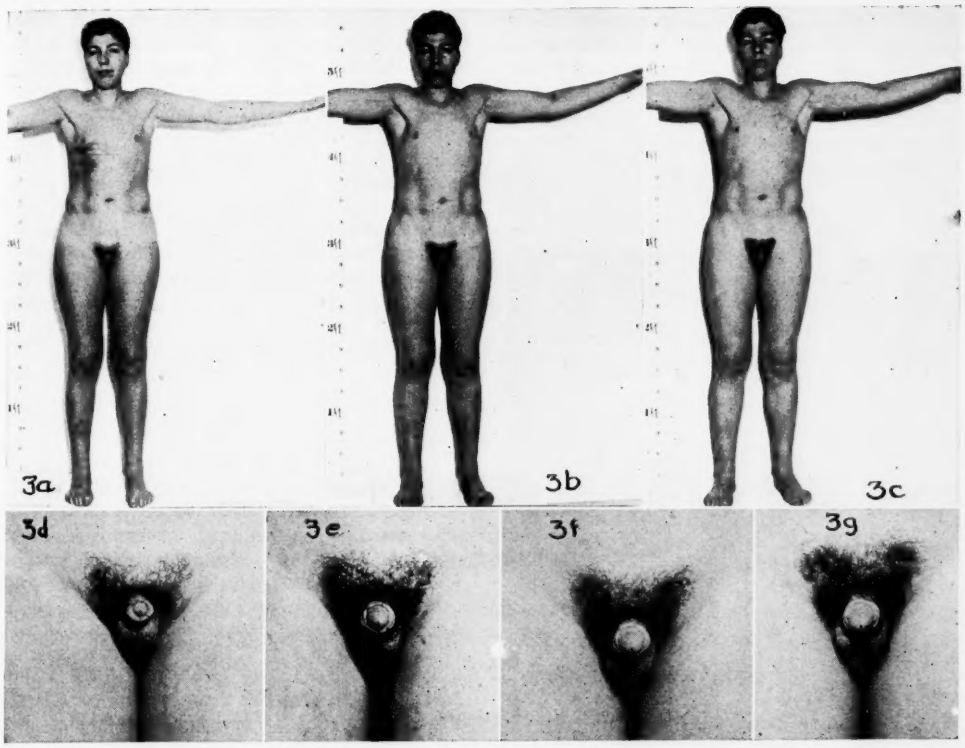


Fig. 3. PREADOLESCENT EUNUCHOIDISM. *Case 6. F. V.* age 24, a and d, August 1940; e, Nov. 1940; b and f, Feb. 1941; c and g, April 1941; Aug. 1940 to Nov. 1940, two implants of 117 and 122 mg. each of methyl testosterone, Nov. 1940 to Feb. 1941; one implant of 600 mg. methyl testosterone; Feb. 1941 to April 1941, 30 mg. methyl testosterone orally per day.

chief complaint was lack of sexual development which had first been noted when he was 13 or 14 years old. Scant pubic hair had appeared at that time and the patient had masturbated occasionally, but with the ejaculation of only a very slight amount of secretion. Axillary hair appeared at the age of 18, simultaneously with a moderate spurt in body growth. Since he was 21 years of age, he had not masturbated and had had nocturnal emissions every 3 or 4 months with very scant secretion. He had had a few injections of testosterone propionate at weekly intervals which had caused some erections. He had never shaved.

The patient was 66¾ in. tall and weighed 155 lb. His extremities were disproportionately long. He looked younger than his stated age and his voice was high-pitched. He had scant axillary and pubic hair and no beard or other body hair. The blood pressure was 100 systolic and 60 diastolic. The penis was small; it measured 4 cm. from pubic bone to tip and 6½ cm. in circumference. The testes were small and soft; the right measured 2½ × 1¼ cm. and the left 1½ × 1½ cm. The prostate was about two-thirds normal size. Laboratory investigation revealed a relative lymphocytosis and a B.M.R. of −18%. Results of roentgenograms of the skull were normal. The bone age was 16 years (chronological age 24 years).

The patient was transferred to the University of California Clinic and on August 8, 1940, he received an implant of 17 pellets of methyl testosterone, or a total of 117 mg. The effects were noticeable the next day and reached a peak of 4 to 5 erections daily 10 days later. A definite waning was noted after 5½ weeks. On September 19, 1940, a second implant was given which totalled 122.9 mg. in 14 pellets. The reaction was similar to that of the first implantation. The effect lasted 6 weeks.

On November 7, 1940, a third implant of 600 mg. of methyl testosterone was placed in the subcutaneous tissues of the back. This large amount, consisting of 3 tablets of 200 mg. each, was given in order to determine whether augmented response would be obtained and whether such stimulation would be maintained for a much longer time. Two days after the implantation the patient began to have almost continuous partial priapism which lasted for a period of 7 to 10 days. The sexual stimulation gradually diminished and had subsided entirely by January 25, 1941, approximately 11 weeks after the implant. The patient remarked that it had "definitely run out." The length of his penis was 5¾ cm. (an increase of 1¾ cm.); circumference was 8¼ cm. The right testis remained the same whereas the left had enlarged from 1½ × 1½ cm. to 3 × 1½ cm. Other effects noted were: occasional nocturnal emissions, increase in general strength and more vigorous growth

of beard and body hair. It is interesting to note that on implantation therapy alone the B.M.R. had risen from −18% to −2%.

Since the benefits derived from the large implant had evidently subsided in about 11 weeks, the effects of small and large implants were compared with those of methyl testosterone administered orally. Accordingly, on February 6, 1941, oral treatment was begun with a dose of 30 mg. daily. Within the first 48 hours, the patient experienced frequent erections which have since occurred daily. Four nocturnal emissions occurred within the first 3 weeks and the relaxed penis had increased 1 cm. in length. The patient had gained 3 lb.

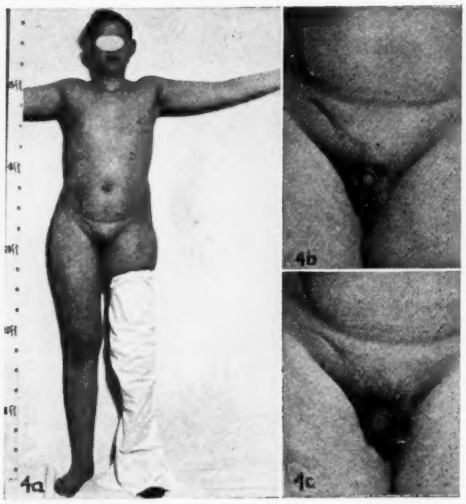


Fig. 4. PREADOLESCENT EUNUCHOIDISM. *Case 7. E. N.* age 21; a and b, Jan. 30, 1941; b, April 12, 1941; average dose of methyl testosterone was 45 mg. per day.

This patient had gained 9 lb. in 2 months on oral testosterone therapy alone. During 8 months of male hormone treatment, he had gained 20 lb. and had grown 1½ in. although he was 24 years old. After 2 months of oral therapy, his penis had grown slightly longer, his testes were perhaps slightly larger and his voice had deepened. His prostrate was considered of normal size. His blood pressure, which had been 100/60, had risen to 120/70. Although he had had considerable libido, he had refrained from masturbating because someone had told him "it was the wrong thing to do." He volunteered a preference for oral over implant therapy because under the former he felt stronger and experienced more frequent erections.

Since in *case 1*, 370 mg. of clinically inactive pellets were removed 4 months after an 800 mg. implant had been given, it was deemed advisable to ascertain whether any crystalline material had remained at the site of the 600 mg. implant in this case. Accordingly, in April 1941, 5 months after the implantation and fully 2 months after cessation of its activity, the remnants were removed. After drying they weighed 155 mg. As in the previous case in which large pellets had been used, considerable fibrous tissue reaction around the implant was demonstrable which no doubt interfered with their complete absorption. However, no abscess had been formed.

*Case 7. E. N.* (Office No. 841) (not previously reported) (fig. 4-A, B, and C). A 27-year-old clerk was first seen on January 25, 1941. His chief complaint was lack of sexual development. Past history revealed that his left leg had been amputated at the age of 23 because of an osteomyelitis following an accident. Sexual retardation had been noted first at the age of 15 when the patient had tried to masturbate but had been unable to achieve an orgasm. He had had occasional erections since that time. His family doctor had informed him that his right testicle was "black" at birth. When the patient was 18 years of age, the same doctor had attempted to bring down the undescended testicle but had not been successful. The patient shaved about once each month.

The patient was tall (71¾ in. without shoes) and had disproportionately long extremities. He weighed 167¼ lb. undressed and had moderate obesity of the trunk with fullness of the breasts but no true gynecomastia. The skin was smooth and had a mottled appearance. He looked younger than his age and his voice was high-pitched. No beard was apparent, and axillary and pubic hair was scant. The penis was small and almost buried in the fat of the mons veneris. It measured 4¾ cm. in length and 7¼ cm. in circumference. The scrotum was small and contained a pea-sized, soft tissue mass on the right. The left testicle measured 3 by 1½ cm. but part of this appeared to be a varicocele. No prostatic tissue could be felt. Blood pressure was normal at 120/70. Laboratory examinations showed a relative lymphocytosis and a B.M.R. of −12%. The bone age was 17 years (chronological age 27 years).

Oral administration of methyl testosterone in doses of 25 mg. twice daily was begun on February 1, 1941. Within 2 days the patient had erections twice a day and he masturbated successfully within the next 2 weeks; the ejaculant consisted of 3 or 4 drops. After 3 weeks of therapy he complained of considerable gastric irritation. The medicine was discontinued for 5 days. Loss of sexual stimulation occurred after 2 days. After resuming the treatment the gastric irritation did not recur.

During 2½ months of oral testosterone therapy the patient gained 8 lb. The penis grew almost 2 cm. in length and 3 cm. in circumference. In this short time no noteworthy change was detectable in the testes; the scrotum, however, was larger and appeared more mature. The prostate, which could not be felt before onset of treatment, was considered about one-fourth of normal size. The voice had deepened somewhat. The dose varied from 30 to 60 mg. per day; the daily average was about 45 mg. On a daily dose of 30 mg. the patient experienced only one erection a day and occasionally none at all. On a dose of 50 to 60 mg. daily, erections occurred 2 or 3 times a day.

## DISCUSSION

*Cases 1, 2* and *6* received several implantations of tiny pellets in doses varying from 103 to 195 mg. per

implant. Subsequently, in each of them, this method was compared in duration and effectiveness with one massive implantation consisting of 200 mg. tablets and totalling 800 mg. in *cases* 1 and 2, and 600 mg. in *case* 6. The latter procedure required a minor surgical operation whereas the former was more simply accomplished by introducing the small pellets through a large bore needle.

The assumption was that the duration of effect would parallel fairly closely the size of the dose; in other words, that an implant 5 times as large would last 5 times as long. It is at once apparent that such was not the case. In *case* 1, 800 mg., namely 5 times the average dose of the smaller implants, were effective only 3½ months instead of the 7½ months anticipated; an average dose of 160 mg. remained actively effective for 6 weeks. Unfortunately, *case* 2 was called to an occupation 3000 miles away shortly after he had received the implant of 800 mg. We are forced to rely on his statement to another observer that the beneficial effects were still present 2 months later. The benefits derived from the implant of 600 mg. in *case* 6 were evidently exhausted in about 11 weeks. Since 2 small implants which averaged 120 mg. (one-fifth that amount) had lasted 6 weeks each, the 600 mg. implant might have been expected to remain effective for 30 weeks.

The conclusion drawn from these observations is that massive implants fail to accomplish the purpose for which they are intended. We are inclined to attribute this disappointing result to local irritation with formation of connective tissue capsule which prevents complete absorption. This explanation is corroborated by the discovery of 370 mg. of pellet remnants in *case* 1, and 155 mg. in *case* 6 which in both had ceased to be effective. Thus, from one-fourth to one-half of the implanted material had been wasted.

Inasmuch as the only factor in favor of the large implants, namely the assumption that such implants might be necessary only two times a year instead of every month or two, was not realized but rather an added inconvenience was occasioned by minor surgery instead of simple introduction through a large bore needle, we are inclined to discontinue the use of this method in clinical practice.

In consideration of the effectiveness of oral testosterone therapy, it is to be noted that only one of our patients (*case* 7) received this type of therapy alone, and, at the time of this report, only for two and one-half months. Although the patient was 27 years old, marked subjective and objective benefits were apparent even in this short time. He gained 8 lb., his voice deepened, his penis enlarged considerably and his prostate became palpable (fig. 4). The average dose of methyl testosterone during this period was 45 mg. daily.

In *case* 6 it was possible to compare the effectiveness of methyl testosterone administered orally with that of methyl testosterone implanted in small and large doses. Oral administration of 30 mg. daily was sufficient not only to maintain the benefits derived from the implantations but also to evoke further improvement. The effectiveness of the large implant lasted 11 weeks. During a similar period the patient would have required 2310 mg. orally, or about four times the amount. The effects of the smaller implants, which averaged 120 mg. each, lasted 6 weeks. During a similar period the patient would have required 1260 mg. by oral administration, or about 10 times the dose All 3 procedures were successful, but it is obvious that the smaller implants were the most economical as regards the amount of material used.

In *cases* 3, 4 and 5, each of which had been observed for several years, a comparison was possible of the effects of testosterone propionate administered parenterally, of implants of the tiny pellets of methyl testosterone averaging about 150 mg. and of methyl testosterone administered orally. In each instance the severe eunuchoidism was strikingly relieved by parenteral therapy. In each instance this improvement was maintained and to some extent augmented during the implantation regime. In each instance the trend toward adult male characteristics and potentialities was preserved and further advanced by male hormone administered orally. Obviously, from the patient's standpoint the ingestion of tablets is simpler and more convenient than implantation. In addition the patients stated that oral treatment provided a more uniform stimulus from day to day while in implantations the stimulus reached a peak and then subsided gradually.

The dose of testosterone required to maintain a normal status which already has been achieved by parenteral therapy is from three to ten times greater by oral administration than by implantation. Experience with these three patients has demonstrated that between five and six times the amount used in implants is necessary for parenteral administration. Therefore the maintenance dose required in oral therapy would seem but little more (two or three times at the most) that that required parenterally.[5] If further experience substantiates this impression, then oral treatment will be not only more convenient but also less expensive than the other forms of treatment, especially if the patient must pay the physician for injections. A comparison of the expense of implant therapy is difficult since the cost of the pellets is not known. The physician's charge for the implantation procedure must also be considered.

[5] McCullagh (4) and Byron and Katzen (7) report that the oral requirement was between three and four times the dose effective parenterally.

Experience in myxedema has established that the maintenance dose of thyroid substance is about one-half to two-thirds of that originally required to elevate a patient's basal metabolic rate to normal. For example, the dose may be raised gradually from ½ to 4 grains daily until optimal effects have been achieved. The improved status can then be maintained by a dose of 2 to 3 grains daily. Similarly, in severe eunuchoidism, larger doses of testosterone are necessary to initiate striking improvement than to maintain the results achieved. Thus, in our experience, *case 7* required an oral dose of about 45 mg. daily to initiate definite subjective and objective improvement. When, optimal effects have been attained, a smaller amount namely 20 to 30 mg. daily, will probably be sufficient to maintain him adequately.

McCullagh (4) and Byron and Katzen (7) have found that continued oral therapy requires progressively increasing doses. McCullagh ascribes this to an increasing ability of the liver to metabolize (or inactivate) methyl testosterone. We have not had this experience, probably because we have used oral therapy for only five months. In none of our patients has an increased dose become necessary. In one of them (*case 5*) a diminished dose of 10 mg. daily sufficed to maintain normal sexual activity.

As stated previously, we abandoned assays of androgen excretion because we considered them unnecessary both for purposes of diagnosis and as a check on treatment. It is interesting to note in this connection that Dorfman and Hamilton (8) in a recent paper on the rate of excretion of urinary androgens after administration of testosterone propionate orally, parenterally and by implantation, report that oral doses were excreted most promptly and produced no clinical benefit. They concluded that the hormone was rapidly inactivated. The lack of clinical benefit must, in our opinion, be ascribed to the use of the propionate which is ineffective orally. The methyl compound is unquestionably potent by mouth and apparently not readily inactivated.

## SUMMARY

Seven patients with severe primary hypogonadism ('preadolescent eunuchoidism'), all over 21 years of age, have been observed for a sufficiently long period of time to permit a critical appraisal of parenteral, implantation and oral administration of testosterone compounds.

In a previous paper (1) it was shown that the implantation of tiny pellets of methyl testosterone, introduced through a large bore needle in doses of between 100 and 200 mg., was satisfactorily effective clinically. Such implants remained active for about 6 weeks. The dosage by this method was only one-sixth of that required parenterally.

In three cases of the present series the effectiveness of such small implants was compared with single massive implants of 600 to 800 mg. Contrary to expectations, the active stimulation was not prolonged in direct ratio to the size of the dose. The pellets ceased to be active much sooner than was anticipated. In 2 of the 3 cases, one-fourth to one-half of the original implant was recovered subsequently. It had evidently been rendered non-absorbable by formation of a connective tissue capsule. Large implants, therefore, were disappointing both as regards duration of effect and wastage of material. Furthermore, massive implants necessitate a minor surgical operation, which does not seem justified by sufficiently additional benefits.

Methyl testosterone by mouth is surprisingly effective in maintaining the improved status previously attained by parenteral or implantation methods. Indeed, the response may be augmented both subjectively and objectively. The dose required is about two to four times the intramuscular dose. It is the simplest, most convenient and possibly the most economical mode of therapy.

In cases of severe eunuchoidism in adults, the initial oral dose required is between 40 and 75 mg. daily. Maintenance doses as a rule are between 10 and 30 mg. daily.

Oral therapy by itself produces gain in weight, elevation of the basal metabolic rate, growth of the external genitalia and prostate, more vigorous growth of sexual hair, deepening of the voice, increased libido and frequency of erections, and increased strength, endurance and mental and emotional animation.

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# Stilbestrol Induced Testicular Degeneration in Hypersexual Males

## [Stilbestrol and Hypersexualism]

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IN 1938 DODDS (1, 2, 3) synthesized stilbestrol (4, 4-dihydroxy-alpha-beta-diethyl stilbene) which was subsequently demonstrated to have the estrogenic qualities of natural estrogens, even though it is chemically unrelated to them. Stilbestrol has been administered with beneficial effect in varying dosage to human females exhibiting the ovarian deficiency syndrome (4) and has also been used to advantage in suppressing menstruation (5) and lactation (6). The incidence of toxic effects from stilbestrol administration has varied from under 5% to over 50% (4, 7, 8) but detailed investigations for disturbed physiological function have failed to determine a pathological cause or causes for its toxicity (9, 10). It has been shown (11) that the human body has no defensive mechanism to inactivate or diminish the estrogenic activity of stilbestrol. To date stilbestrol has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association (12), nor has it been released as a therapeutic agent by the Federal government.

The reports of von Haam et al. (13) present a critical analysis of the clinical, laboratory and experimental results obtained with stilbestrol. von Haam found that the administration of stilbestrol to human females markedly reduced the gonadotropic content and increased the estrogenic content of the urine. Their studies reveal that from 10% to 30% of the administered stilbestrol is excreted in the urine and feces during the first 10 days following its administration. Excretion of stilbestrol in the urine begins immediately after its administration, reaches its highest levels on the third to fifth day and decreases rapidly to a small amount which can then be found in the urine up to the twentieth day. Their studies also show that there is a marked diminution in the basophil cell count in the pituitary of rats receiving stilbestrol (14). In both experimental animals and in the human being there is evidence that stilbestrol depresses anterior pituitary gonadotropic function.

There has been no detailed report on the action of stilbestrol on the human ovary. Karnaky (15, 16) has administered stilbestrol to more than four hundred patients. He found that it took 100 mg. over a period of 20 days to cause the ovaries to atrophy. On gross examination the ovaries appeared smooth and were like the ovaries of a woman at term. On cross-section, the follicular cysts were about one-eighth to one-twelfth the size of the follicular cysts seen in a normal menstruating woman and about one to two mm. in size, usually depending on the amount of stilbestrol administered.

Zondek (17) has demonstrated that the administration of large doses of the natural estrogens to guinea pigs and fowls depresses anterior pituitary function. This depressive effect of large doses of the natural estrogens has been utilized in the treatment of acromegaly (18) and pituitary basophilism (19, 20).

If sustained estrogenic inhibitory effect on anterior pituitary function is desired, sufficient estrogen must be administered at intervals which will maintain a peak curve of estrogenic content in the blood.

It was decided to attempt to depress continuously anterior pituitary gonadotropic function in two cases of male hypersexualism by the administration of stilbestrol. Stilbestrol was selected because we considered it a more potent pituitary gonadotropic inhibitant than the natural estrogens and, further, its oral administration had proven most effective. Five milligrams of stilbestrol was administered orally and daily, this dose being the equivalent of from 25,000 to 30,000 R.U. of estrone.

*Case 1.* A male, age 27 years, married, with one male child, was first examined on November 22, 1939. The patient admitted abnormally early sexual activity, including intercourse with adults at 14 years of age. This excessive sexual behavior continued through adolescence and in the past 7 years the patient had committed sexual offenses

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against female minors which resulted in his incarcerations. He is now serving the maximum prison sentence for a sexual offense committed while on parole from a similar previous conviction. Investigation of his previous confinement in prison reveals that he failed to adapt himself to prison life and was a persistent troublemaker. Shortly after the present commitment he was placed in solitary confinement because of serious insubordinations. When first examined, he was preoccupied with his sexual life and, in spite of the 7-year sentence, had made plans to resume a sexual relationship with an allegedly hypersexual married woman.

The patient was tall, slender and overactive, both physically and mentally. No abnormalities were revealed on physical examination, except as hereafter noted. The penis was unusually large (of maximal negroid dimensions) for a white male and an erection was easily elicited. The testes were of maximal normal size. The scrotum was well developed. Assay of the urine[1] before therapy showed abnormal amounts of male hormone and gonadotropic hormone (table 1).

TABLE 1. URINARY HORMONE ASSAYS OF *Case 1*

| | Before therapy | 53 days after discontinuing therapy; total administered: 565 mg. stilbestrol |
|---|---|---|
| Androgen | 300 R.U. | 180 R.U. |
| Estrogen | 20 R.U. | 30 R.U. |
| APL | 120 R.U. | 75 R.U. |

The patient was given orally 5 mg. of stilbestrol daily for 60 days and 5 mg. every other day during the following 107 days. After 4 weeks' therapy he stated that his sexual responses, physical and mental, were appreciably diminished. His behavior and attitude improved and he had adapted himself to prison routine and discipline. His only complaint was an inability to eat the prison food, which was later found to result from the stilbestrol therapy. His behavior and attitude further improved with therapy and after 60 days of treatment he stated that his sexual reactions had further diminished and an almost complete loss of sexual function had occurred. In 110 days (85 therapeutic days) after 425 mg. of stilbestrol had been administered, the patient's breasts became sensitive and he noted a small, firm mass present beneath each nipple. The mass increased progressively in size and sensitiveness and on the 132nd day after starting therapy, (96th therapeutic day) when 480 mg. of stilbestrol had been administered, a hard, firm mass measuring 6 cm. in diameter and 2½ cm. in thickness was present in each mammary region (21). At this time the penis and testes were approximately two-thirds of the pre-therapeutic size. The patient reported an absence of libido and stated that masturbation did not produce an erection or an emission. The penis remained flaccid during examination. More marked improvement in demeanor and adaptability to prison routine was reported. Other than slight loss of weight, there was no evidence of toxic effect from the stilbestrol.

Testicular biopsies of each testis, performed on November 7, 1940 after 153 days of therapy (106 therapeutic days), when 530 mg. of stilbestrol had been administered, revealed "a generalized degenerative process involving the specialized epithelial cells. There was no evidence of normal cell growth and not a single tubule displayed cellular development to the spermatid stage. There was a reduction in the number of interstitial cells. The cellular structure showed complete degeneration with only a single layer of necrotic cells lining the basement membrane. The lumen of the tubule was practically empty"[2] (fig. 1, 2).

On receipt of this report therapy was discontinued on the 166th day (113 therapeutic days) after 565 mg. of stilbestrol had been administered. In the 7 weeks following discontinuance of therapy the patient experienced no sexual desires or erections except in the last 2 weeks when he had four morning erections which disappeared on voiding. The penis had increased slightly in diameter and exhibited turgescence during examination. The testes had diminished in size and were abnormally insensitive to digital pressure. All that remained of the breast hyperplasia was a slight fibrotic nodule under each nipple. The anorexia and distaste for food had disappeared, he was eating normally and had gained weight. His deportment was good.

Urinary assays on January 11, 1941, 53 days after discontinuance of therapy, showed an increase of 50% in estrogen and a 33% decrease in androgen and APL (table 1).

Testicular biopsies were again performed[3] on January 20, 1941, 62 days after therapy was discontinued, and this examination disclosed that "the tubules contained cells in great activity. Every stage of cell division was again seen as in the normal. Some edema and vacuolization were, however, present. The lumen was filled with maturing spermatids and spermatozoa (fig. 3). Pressure atrophy of a seminiferous tubule by surrounding regenerating tubules was also shown" (fig. 4). It was Doctor Charny's opinion, based on the biopsy studies, that the number of active tubules in the regenerated testis would be diminished.

On January 23, 1941, 65 days after discontinuing therapy, the patient reported an absence of natural erections and stated that an induced erection was difficult to obtain and emission was very scant.

One hundred twelve days after the withdrawal of therapy the patient began to experience a return of sexual desire and in the previous 2 weeks two spontaneous erections of short duration had occurred. The unerected penis measured 4 in. and on examination erected slightly and then measured 4½ in. The patient requested that stilbestrol therapy be resumed at 5 mg. daily, orally administered, because he had noted that sexual activity declined more rapidly with daily administration than with alternate daily dosage of 5 mg. of stilbestrol. Therapy was re-

[1] Assay method employed in *case 1*. The method of assay employed in *case 1* was the same as reported by Arthur Steinberg for prolans and estrogens in the American J. Obst. & Gynec., 1941, page 979. The method for assaying the androgens was essentially that of Gallagher, Koch and Dorfman in the Proc. Soc. Exper. Biol. & Med., 33: 440. 1935.

[2] Biopsy was performed by Doctor Charles W. Charny.

[3] By Doctor Charny.

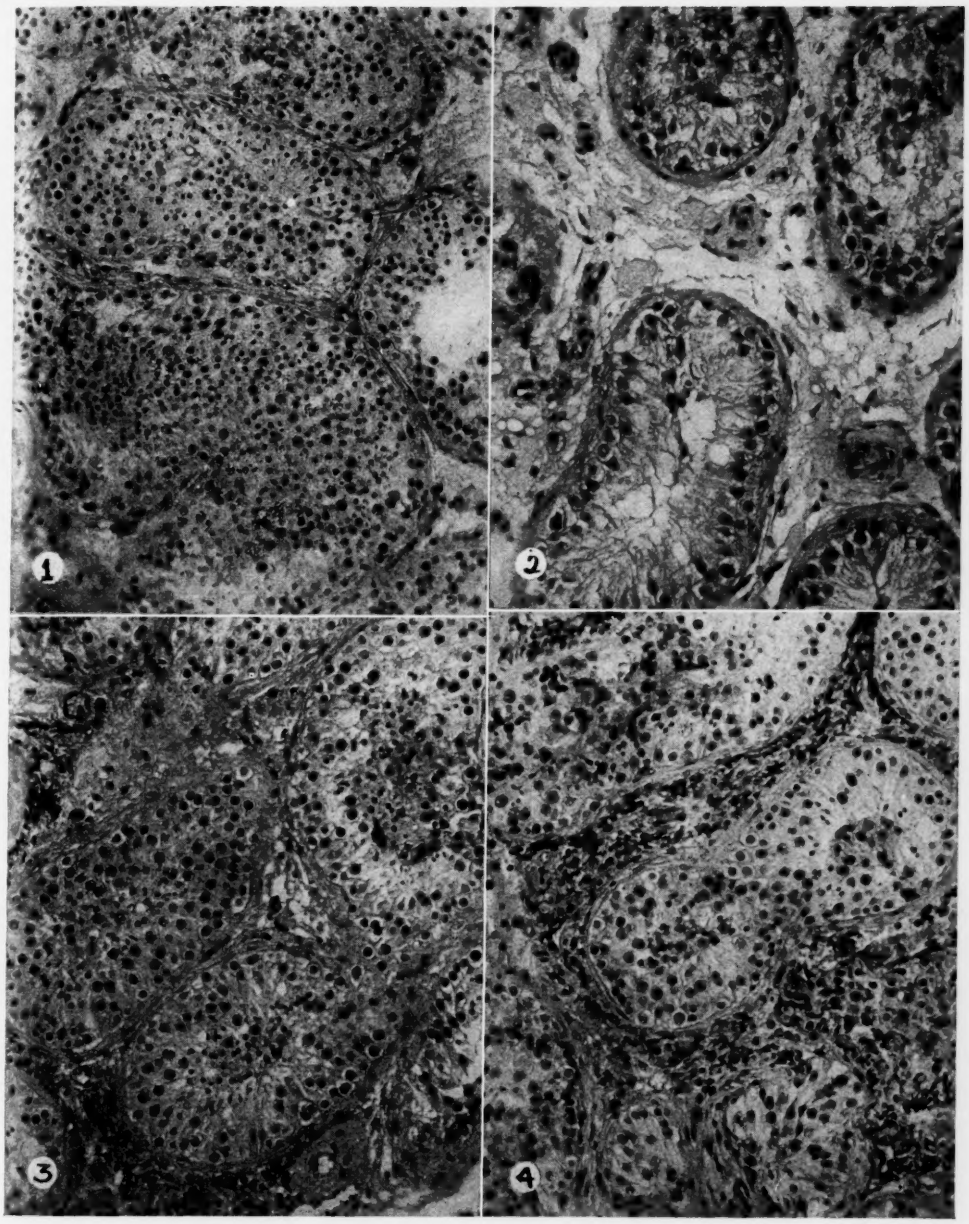


Fig. 1. Normal. Fig. 2. *Case 1.* Complete degeneration. 11/7/40, after 530 mg. of stilbestrol. ×268. Fig. 3. *Case 1.* Regeneration after withdrawal of stilbestrol therapy. 1/20/41, 62 days after cessation of therapy. Total stilbestrol administered: 565 mg. ×190. Fig. 4. *Case 1.* Regeneration, showing pressure on tubules. 1/20/41, 62 days after cessation of therapy. ×190.

sumed on the 112th day after discontinuing therapy, 5 mg. of stilbestrol being orally administered daily.

*Case 2.* A male Negro, age 12 years, was first examined on July 30, 1940. The patient was referred because of precocious sexual activity and sexual advances to female minors during the past year and a half. He experienced frequent daily erections and erections were also observed during sleep. His sister, age 4 years, was the subject of his persistent sexual advances and he required constant su-

pervision since he constantly sought seclusion with females, particularly small children. He was generally discontented and uncooperative in the home and avoided male companions. He procured sexual articles, such as condoms and syringes.

Examination revealed a prematurely adolescent boy, excessively tall and slender for his age, extremely restless, uncooperative and hyperactive. Systemically the findings were normal, except as hereafter noted. The unerected penis was 4½ in. long and was easily excited to an erection. The testes were proportionately enlarged. The scrotum was large. Axillary, pubic and body hair were excessive for his age. Facial hair growth was adolescent in type. His voice was deep in pitch.

Five mg. of stilbestrol was ordered to be given orally every other day. The patient knew the purpose of therapy and cunningly disposed of the medicine for some weeks. When he failed to improve, as did the previous case, this deception was discovered and the patient alleged that the medicine had produced nausea. His treatment was then directly supervised by his mother and he received 5 mg. of stilbestrol daily, without developing nausea. After 6 weeks of 5 mg. stilbestrol daily, when a total of 210 mg. had been administered, a diminution in sexual activity was noted. His interest in females was appreciably lessened and the patient no longer annoyed his sister and other small girls. He was more contented at home. Irritability and restlessness were less marked. He began to play with male neighbors, indulged in normal boyish activities and entered group play.

The patient was under the observation of the referring physician and was reexamined at the end of 75 days of stilbestrol therapy, 5 mg. per day, when a total of 375 mg. had been administered. A marked change in his behavior and attitude was apparent. His sister had lost all fear of him because he had ceased his sexual approaches. His general physical appearance was excellent. There had been a weight gain of 5½ lb. The penis had diminished to 3 in. in length, was smaller in diameter, and remained flaccid after examination whereas it previously became erect. There was a measurable decrease in the size of the testes and their sensitiveness was diminished. The nipple and areola had become deeply pigmented. A gynecomastia the size of a twenty-five cent piece was observed in both breasts. Histological examination[4] of the breast tissue showed a marked increase in the periductal pale staining connective tissue. The epithelium lining the ducts had increased to four more layers in thickness and the tissue showed the effects of estrogenic stimulation.

Testicular biopsy[4] on December 27, 1940, after 75 days of administration of 5 mg. stilbestrol daily, showed incomplete degeneration. "The tubules were very compact and there was relatively little interstitial tissue present. The epithelium lining the seminiferous tubules showed cloudy swelling, evidence of degeneration, and nowhere was spermatogenesis advanced to the stage of spermatid formation. The tubules showed the same necrotic changes as in *case* 1,

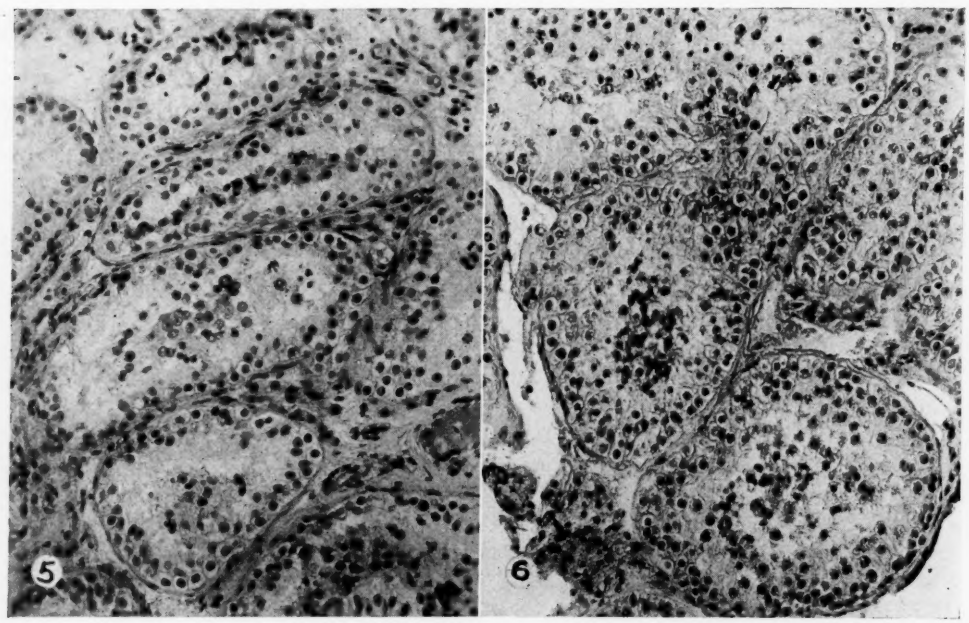


Fig. 5. *Case 2.* Moderate degeneration. 12/27/40. After 375 mg. of stilbestrol. Fig. 6. *Case 2.* Regeneration after cessation of stilbestrol therapy. 2/13/41, 48 days after cessation of therapy. ×190.

[4] By Doctor Charles F. Geschickter who also studied our cases of gynecomastia produced by the natural estrogens.

except that the degenerative process was not as advanced. There was a single layer of cells adjoining the basement membrane and a great deal of cellular material being extruded into the lumen" (fig. 5).

Therapy was discontinued at this time. In a letter of January 10, 1941 his mother wrote, "His disposition seems changed. He is not so nervous as he was formerly. Erections have ceased to occur, night or day. The penis continues to shrink in size."

The patient was again examined on February 13, 1941, 48 days after discontinuance of therapy. He had continued to improve until the previous week when there was a return of erections and the penis became reactive. The penis measured 4 in., an increase of 1 in. since discontinuing therapy. The gynecomastia had disappeared.

Testicular biopsy performed[5] on February 13, 1941, revealed "a regenerative process as evidenced by an increased number of layers of cells. However the growth process was not so far advanced as in *case 1*. Relatively fewer spermatids were present and vacuolization was more marked. The improvement over the degenerative process was very apparent" (fig. 6).

Urinary assays,[6] 51 days after discontinuing therapy and with the return of symptoms, revealed no estrin nor prolan, androgen, 52 I.U. per 24 hours (high normal).

Therapy was resumed on March 8, 1941, 61 days after discontinuing therapy. In a letter of March 19, 1941 his mother wrote, "He has become quite unruly and insisted on following his sister. He has the old difficulty of going to bed and going to sleep. I believe that the medicine is beginning to take effect as the patient is at least remorseful at his misconduct. Nightly penile erections no longer occur."

## DISCUSSION

A study of the effect of orally administered stilbestrol on the human testes in 2 cases of hypersexualism, an adult, age 27 years, and a boy, age 12 years, with precocious genital development, indicates that oral administration of 300 mg. of stilbestrol, 5 mg. daily, should initiate degenerative changes in the seminiferous tubules of the testes and suppression of spermatogenesis. In the adult 530 mg. of stilbestrol produced complete degeneration and in the boy 375 mg. produced moderate degeneration. The degree of testicular degeneration was proportionate to the dosage, frequency and total quantity of stilbestrol administered.

Clinical improvement was first noted in both cases after 150 mg. of stilbestrol had been administered. This beneficial effect of stilbestrol on the hypersexual syndrome became more evident as therapy was continued. The physical and mental restlessness and intractability disappeared and the patients became more cooperative and normal in personality and behavior. The hypersexual reactions were inhibited to subnormal levels and this was eventually succeeded by impotence, diminution in the size of the penis and testes and the development of gynecomastia.

It has been interesting to confirm in these cases our previous conclusion (23) that a significant relationship exists between the onset of estrogenic breast reaction and clinical improvement in both males and females treated with the natural estrogens. In major ovarian deficiencies, as severe menopausal depression or migraine, treated with estradiol benzoate, the symptom state was often not controlled until estrogenic breast reaction was established, at which point the dosage could be diminished or therapy discontinued. In cases of severe recurring migraine in males treated with estradiol benzoate (24) we have similarly observed that relief and control of the migraine attacks did not occur until gynecomastia developed and resolution of the breast reaction was frequently followed by a return of symptoms.

In these cases the hypersexual symptoms were absent and testicular degeneration was present while stilbestrol-induced breast hyperplasia existed. Return of penile reaction and regeneration in the seminiferous tubules coincided with resolution of the induced breast hypertrophy. This regenerative reaction of the testes followed discontinuance of therapy and was evident in *case 2* in 48 days and in *case 1* in 62 days after stopping therapy.

The ideal therapeutic program for male hypersexualism would induce an inhibition of anterior pituitary gonadotropic function commensurate with the androgen and APL excess and maintain testicular function at a low normal physiological level without destruction of spermatogenesis. It therefore seems advisable to correlate the clinical, histological and biological findings in these cases in order to determine an estimated daily and total dosage of stilbestrol required in treating male hypersexualism. The total amounts of stilbestrol administered here produced aspermia and extensive degeneration of the seminiferous tubules in a comparatively short period of therapy. Testicular regeneration occurred after discontinuance of stilbestrol therapy so that irreparable damage to testis function did not result. The present total dosage of stilbestrol is, therefore, within safe limits.

It appears that an adult male possesses a greater degree of regenerative power in the testis than the precociously developed 12-year-old male, even when the adult is given almost twice as much stilbestrol.

The following criteria of the effects of stilbestrol therapy in male hypersexualism have been determined in this study.

[5] By Doctor Charny.

[6] Assay method employed in *case 2*. Technic for determination of androgens in urine by Dr. D. R. McCullagh and Dr. R. Guillet from the Cleveland Clinic Quarterly, 6: 95, 1939. Technic for determination of estrogens in urine by same authors and same reference, as above for androgens. Technic for determination of prolan in urine by Dr. B. Zondek.

1. The effect of stilbestrol on the hypersexual symptoms and the reduction in the size of the genitals
2. The induction of gynecomastia
3. Hormone assays of androgens and gonadotropins
4. Testicular biopsies.

When hormone assays and testicular biopsies are not available to check the effect of stilbestrol therapy, it is the author's opinion that stilbestrol therapy should be stopped with the onset of breast reaction. If the hypersexual symptoms reappear, therapy should be resumed and continued until favorable effect is again noted.

These findings confirm our pre-therapeutic hypothesis that it is possible to depress anterior pituitary gonadotropic function in the male and, secondarily, to affect male hormone secretion by the administration of stilbestrol in large doses. Though here used to advantage, the possibility of a criminal usage of stilbestrol to normal males was suggested by a female patient.

Both cases have exhibited a return of sexual function with testicular regeneration, though the degree of return of sexual response was initially subnormal in both cases. As therapy was further withheld, early manifestations of the hypersexual state appeared and stilbestrol therapy was resumed at the end of 112 days in *case 1* and 61 days in *case 2*.

## CONCLUSIONS

Oral stilbestrol therapy has caused disappearance of the hypersexual state and a total lack of sexual impulses in a male sexual criminal, age 27 years, and in a precociously developed male, age 12 years. Three hundred seventy-five and 565 mg. of stilbestrol, orally administered, in the main, 5 mg. daily, produced moderate and advanced degenerative changes in the seminiferous tubules (therapeutic sterility) in the human male gonad.

Discontinuance of stilbestrol therapy for 9 to 16 weeks resulted in regenerative reaction of the degenerated seminiferous tubules and reappearance of sexual impulses at a subnormal level. In view of the serious social problem involved in these cases, stilbestrol therapy was resumed as a precautionary measure when the patients exhibited interest in sexual matters and the associated restlessness and activation of the hypersexual state. Stilbestrol therapy will be maintained until from 300 to 400 mg. are administered or until gynecomastia reappears and either hormone assays or testicular biopsies or both indicate the full desired inhibitory effect on sexual function.

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# Results of Treatment in 40 Selected Cases of Cryptorchidism

[Cryptorchidism]

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FOR MANY YEARS the management of cryptorchidism has been an intriguing problem to the medical profession. The four major concerns have been with (*a*) anatomical restitution of the affected organs to a normal position in the scrotum, (*b*) proper development of the affected organs, (*c*) normal functional results so as to insure both fertility and the elaboration of male sex hormone, and finally (*d*) the possibility of degenerative and malignant changes occurring in testes occupying a faulty position, or in testes the position of which has been corrected.

Up to recent years the most satisfactory approach to proper placement of the testes was surgical, even though many surgeons have expressed dissatisfaction with the frequency of lack of development following surgery. Numerous reports of operative results have been recorded in the literature, the percentage of cures ranging from 42 to 92%.

Impetus to an understanding of the mechanism of testicular descent and the treatment of cryptorchidism was given by the fundamental discovery in 1928 of Aschheim and Zondek (1) that a gonad stimulating substance was present in pregnancy urine. In 1929, Engle (2) showed that an increase in rate of growth of the sex organs of the immature rat could be produced by injections of pregnancy urine. With these findings in mind, Schapiro (3) in 1930 used a water-soluble extract of pregnancy urine in the treatment of genital hypoplasia and cryptorchidism. More extensive use of extracts of pregnancy urine in the management of cryptorchidism followed Engle's (4) demonstration that testicular descent could be produced in monkeys with delayed puberty by injecting pregnancy urine or the active principle of the anterior pituitary gland. Since then there has accumulated an extensive literature dealing with the endocrine therapy of cryptorchidism. This has been reviewed by Bigler, Hardy and Scott (5) as well as by Nixon. A wide divergence of opinion exists among observers concerning the efficacy of hormonal therapy, and one finds cures recorded in from 19 to 72% of the cases treated. These conflicting figures have created considerable skepticism. Fortunately with the present tendency to more careful selection of patients, there has been a decrease of the enthusiasm shown by early observers, and cures are being recorded now ranging up to 33%.

In this communication, the results in an additional 40 cases are presented. Great care was exercised in the selection of patients in order to eliminate all of those with pseudo-cryptorchidism. It is probable that in some of the early series reported by others, no serious attempt was made to differentiate pseudo from true cryptorchidism.

In our experience, it was found frequently that a strong cremasteric reflex caused the testicles to retract into the inguinal canals. This reflex appeared readily in boys who were nervous or apprehensive or cold, when the genitalia were palpated, when the inner aspect of the thigh or scrotum was stroked, or sometimes more or less spontaneously when the examiner approached the patient. At least half of the patients referred to us with the diagnosis of cryptorchidism were of this character, and were dismissed without treatment. At times, it was necessary to examine such patients on several occasions. It was found that the application of hot wet towels over the pubic region facilitated the examination and often proved helpful. By such careful and repeated examinations, it was possible to eliminate from the present series all patients except those with true cryptorchidism.

This report is concerned with data pertaining to 40 cases so selected. Of these, 26 or 65% had unilateral and 14 or 35% had bilateral cryptorchidism, a total

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of 54 undescended testes. The location of these testes is shown in table 1. In 26 unilateral cases, 18 were on the right and 8 on the left side; 5 were not palpable (intra-abdominal), and 21 were located in the inguinal canal. In the 14 bilateral cases, only 2 were intra-abdominal, the remaining 12 being located in the inguinal canal.

TABLE 1. LOCATION OF TESTICLES BEFORE INSTITUTION OF THERAPY IN 40 CASES OF CRYPTORCHIDISM

| Side | Right | Left | Bilateral |
|---|---|---|---|
| Not palpable | 2 | 3 | 2 |
| Upper-canal | 1 | 1 | 0 |
| Mid-canal | 13 | 2 | 10 |
| Lower-canal | 2 | 2 | 2 |
| Total | 18 | 8 | 14 |

No attempt was made to exclude a patient from this study because of age. In table 2 is seen the distribution of this series according to age in years. The youngest was a boy of 5, the oldest one of 17, the former with bilateral, and the latter with unilateral cryptorchidism. Reference to table 2 also reveals that 29 (75%) were between the ages of 8 and 13, 8 (20%) between the ages of 5 and 7, and the balance of 3 (7%) between the ages of 14 and 17.

TABLE 2. THE NUMBER OF PATIENTS WITH GOOD RESULTS FOLLOWING HORMONAL AS WELL AS SURGICAL THERAPY AT DIFFERENT AGES

| Age in years | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of cases | 2 | 3 | 3 | 4 | 3 | 6 | 4 | 7 | 5 | 0 | 1 | 1 | 1 |
| Cases of successful hormonal therapy | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 3 | 1 | | 0 | 0 | 0 |
| Cases of successful surgical therapy | 0 | 1 | 1 | 1 | 1 | 3 | 0 | 0 | 1 | | 0 | 0 | 0 |
| Total complete successes | 1 | 2 | 1 | 3 | 3 | 4 | 1 | 3 | 2 | | 0 | 0 | 0 |

An attempt was made to classify these patients roughly according to body build. Ten were overweight or stocky, with a definite tendency to feminine bodily contour, 18 were normal, one tall and one short, and 9 thin,

## METHOD OF TREATMENT

All were treated with gonadotropic principle of pregnancy urine (pregnancy urine hormone). The hormone was administered subcutaneously 3 times weekly in doses of 200 R.U. This was increased to 500 U in 3 instances after a few weeks of unsuccessful therapy with the smaller dosage. No difference in effect was observed following this increase. The duration of treatment varied from 2 to 8 months with a grand total of 156 months in the 40 cases studied, an average of 4 months per case. A total of 1999 injections or 430,000 U was given to the entire group, an average of 50 injections or 10,765 U per patient.

*Effect of injections of pregnancy urine hormone on descent of the testicle.* The results of the treatment of cryptorchidism with pregnancy urine hormone were divided into the following 3 groups: (*a*) complete descent when one or both testicles descended into the scrotum and remained there, (*b*) partial descent when a testicle descended from a point high in the canal to a definitely lower position, or in the case of bilateral cryptorchidism when one testicle descended into the scrotum while the other remained relatively fixed, and (*c*) when the position of the testes remained unchanged. Although all patients were observed for many months after treatment was discontinued, none was encountered in whom the testicle retracted into the canal or abdomen after once assuming a scrotal position following hormonal therapy. No difficulty was experienced in arriving at a conclusion regarding the success or failure of therapy.

TABLE 3. SUMMARY OF RESULTS OBTAINED FROM HORMONAL THERAPY OF CRYPTORCHIDISM

| | Unilateral cryptorchidism | Bilateral cryptorchidism |
|---|---|---|
| Complete descent | 6 | 6 |
| Partial descent | 0 | 2 |
| No descent | 20 | 6 |
| Total no. cases | 26 | 14 |

In tables 3 and 4 are presented the results of treatment with pregnancy urine hormone. Only 6 of the 26 unilateral and a similar number of the 14 bilateral cases showed complete descent, a total of 12 successes or 30%. There were no unilateral and only 2 bilateral cases showing partial descent. In both of these, one testicle descended into the scrotum while the position of the other remained unchanged.

Thus there was a total of 12 patients with complete, 2 with partial, and 26 with no descent following hormonal therapy. To the latter group of 26 patients must be added 2 cases of bilateral cryptorchidism in whom only unilateral descent was affected, making a total of 28 cases in which this form of therapy was not followed by complete descent, and for whom surgery was considered. Permission for opera-

tion was refused in 5 unilateral and 2 bilateral cases, and deferred in *case 1* because of the youth of the patient. Thus surgical fixation of the testicle in a normal position within the scrotum was resorted to in 20 patients. Of these, 14 were unilateral, and 6 were bilateral before the institution of hormonal therapy. Actually, however, in *cases* 3 and 36, unilateral descent had occurred following hormonal therapy so that at the time of operation there were in reality 16 cases of unilateral and 4 of bilateral cryptorchidism.

*Results of surgery.* Data concerning the patients on whom operations were performed are presented in table 5. The results of surgery have been indicated as being good, fair, or poor. A good result is one in which the affected testicle is normal in size and remains in a normal position within the scrotum for a long period of time following surgery. A fair result is one in which the testicle retracts to a point high up in the scrotum, while a poor result is one in which the surgically fixed testicle retracts to its original position or one in which definite lack of development exists.

Good surgical results in the strictest sense of the word were not obtained in any of the 4 bilateral cases in this series. The usual course was that some time after surgery, the testes retracted high up in the scrotum or into the lower portion of the inguinal canal. In one instance although the testes were brought down successfully, one was definitely hypoplastic, and thus considered to be a poor result. The results in the 16 unilateral cases may be classified as follows: good, 8; fair, 3; and poor, 5. In the 8 recorded

TABLE 4. DATA ON PATIENTS TREATED WITH PREGNANCY URINE HORMONE

| Case no. | Age | General body build | Testes location before treatment | | Months of treatment | No. of injections | Total R.U. | Testes location after treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Right | Left | | | | Right | Left | |
| 1 | 5 | Normal | I.S. | N.P. | 8 | 102 | 20,400 | I.S. | N.P. | No descent |
| 2 | 11 | Tall | I.S. | M.C. | 4 | 60 | 12,000 | I.S. | I.S. | Complete desc. |
| 3 | 10 | Stocky | M.C. | M.C. | 5 | 72 | 14,400 | I.S. | M.C. | Partial descent |
| 4 | 8 | Normal | L.C. | I.S. | 4 | 56 | 11,200 | I.S. | I.S. | Complete desc. |
| 5 | 7 | Stocky | M.C. | I.S. | 4 | 51 | 10,200 | M.C. | I.S. | No descent |
| 6 | 11 | Normal | M.C. | M.C. | 5 | 66 | 13,200 | M.C. | M.C. | No descent |
| 7 | 10 | Normal | M.C. | I.S. | 4 | 52 | 10,400 | M.C. | I.S. | No descent |
| 8 | 12 | Short | I.S. | U.C. | 4 | 45 | 9,000 | I.S. | M.C. | No descent |
| 9 | 17 | Normal | N.P. | I.S. | 3 | 38 | 7,600 | N.P. | I.S. | No descent |
| 10 | 15 | Normal | M.C. | I.S. | 2 | 27 | 5,400 | M.C. | I.S. | No descent |
| 11 | 9 | Normal | N.P. | N.P. | 4 | 48 | 9,600 | I.S. | I.S. | Complete desc. |
| 12 | 10 | Normal | M.C. | M.C. | 7 | 91 | 18,200 | M.C. | M.C. | No descent |
| 13 | 8 | Normal | I.S. | L.C. | 3 | 39 | 7,800 | I.S. | L.C. | No descent |
| 14 | 8 | Thin | M.C. | I.S. | 3 | 40 | 8,000 | M.C. | I.S. | No descent |
| 15 | 13 | Normal | M.C. | I.S. | 3 | 36 | 7,600 | M.C. | I.S. | No descent |
| 16 | 7 | Thin | N.P. | N.P. | 5 | 66 | 13,200 | N.P. | N.P. | No descent |
| 17 | 13 | Thin | I.S. | N.P. | 3 | 37 | 16,700 | I.S. | N.P. | No descent |
| 18 | 12 | Thin | M.C. | M.C. | 4 | 51 | 10,200 | I.S. | I.S. | Complete desc. |
| 19 | 16 | Normal | U.C. | I.S. | 3 | 38 | 7,600 | U.C. | I.S. | No descent |
| 20 | 12 | Stocky | M.C. | I.S. | 3 | 39 | 7,800 | I.S. | I.S. | Complete desc. |
| 21 | 12 | Stocky | I.S. | N.P. | 6 | 75 | 15,000 | I.S. | N.P. | No descent |
| 22 | 10 | Normal | M.C. | I.S. | 2 | 28 | 5,600 | M.C. | I.S. | No descent |
| 23 | 12 | Normal | M.C. | M.C. | 5 | 65 | 13,000 | M.C. | M.C. | No descent |
| 24 | 6 | Normal | M.C. | I.S. | 4 | 44 | 8,800 | M.C. | I.S. | No descent |
| 25 | 11 | Stocky | M.C. | M.C. | 6 | 78 | 15,600 | M.C. | M.C. | No descent |
| 26 | 10 | Normal | L.C. | I.S. | 2 | 24 | 4,800 | I.S. | I.S. | Complete desc. |
| 27 | 13 | Thin | M.C. | I.S. | 5 | 56 | 11,200 | M.C. | I.S. | No descent |
| 28 | 13 | Stocky | M.C. | I.S. | 4 | 50 | 10,000 | I.S. | I.S. | Complete desc. |
| 29 | 13 | Stocky | I.S. | L.C. | 3 | 38 | 7,600 | I.S. | L.C. | No descent |
| 30 | 5 | Thin | M.C. | M.C. | 3 | 39 | 7,800 | I.S. | I.S. | Complete desc. |
| 31 | 12 | Stocky | M.C. | L.C. | 4 | 50 | 10,000 | I.S. | I.S. | Complete desc. |
| 32 | 6 | Stocky | I.S. | M.C. | 4 | 53 | 10,600 | I.S. | I.S. | Complete desc. |
| 33 | 12 | Normal | M.C. | M.C. | 4 | 52 | 10,400 | M.C. | M.C. | No descent |
| 34 | 10 | Normal | M.C. | I.S. | 3 | 38 | 7,600 | M.C. | I.S. | No descent |
| 35 | 8 | Thin | L.C. | L.C. | 5 | 62 | 12,400 | I.S. | I.S. | Complete desc. |
| 36 | 9 | Thin | M.C. | L.C. | 4 | 50 | 10,000 | L.C. | I.S. | Partial desc. |
| 37 | 11 | Normal | M.C. | I.S. | 5 | 63 | 19,800 | M.C. | I.S. | No descent |
| 38 | 7 | Thin | N.P. | I.S. | 3 | 38 | 9,200 | N.P. | I.S. | No descent |
| 39 | 9 | Stocky | L.C. | L.C. | 3 | 37 | 7,400 | I.S. | I.S. | Complete desc. |
| 40 | 6 | Thin | M.C. | I.S. | 1 | 5 | 1,000 | M.C. | I.S. | No descent |

In tables 4 and 5, N.P. indicates nonpalpable; U.C., upper portion of inguinal canal; M.C., midportion of inguinal canal; L.C., lower portion of inguinal canal; and I.S., in scrotum.

as good, the surgically fixed testes were essentially the same size as those on the opposite sides and continued in their normal scrotal position after surgery had been completed. In the 3 classified as fair, the testes did not retain a normal position but rode high in the scrotum. In the 5 designated as poor, the testes were either hypoplastic or retracted to the position occupied prior to surgery. In one instance the hypoplastic testicle was removed by orchidectomy.

Thus complete testicular descent occurred in 12 of 40 cases of cryptorchidism (30%) following treatment with pregnancy urine hormone. Of the 28 failing to show descent following hormonal therapy, 8 have received no further therapy leaving a balance of 20 in whom surgical fixation of the testicle was attempted. In this latter group, complete descent was affected in 8, making a total of 20 or 50% who were benefitted completely by hormonal therapy alone or by a combination of hormonal and surgical treatment.

TABLE 5. DATA ON PATIENTS IN WHOM SURGICAL FIXATION OF TESTES WAS PERFORMED FOLLOWING UNSUCCESSFUL TREATMENT WITH PREGNANCY URINE HORMONE

| Case no. | Testes location before hormonal therapy | | Total R.U. | Testes location after hormonal therapy | | Condition of testes at operation | | Final result following surgery | |
|---|---|---|---|---|---|---|---|---|---|
| | Right | Left | | Right | Left | Right | Left | Right | Left |
| 3 | M.C. | M.C. | 14,400 | I.S. | M.C. | | N.I.C. | | Fair |
| 5 | M.C. | I.S. | 10,200 | M.C. | I.S. | N.I.C. | | Good | |
| 6 | M.C. | M.C. | 13,200 | M.C. | M.C. | A.I.C. | N.I.C. | Poor | Good |
| 7 | M.C. | I.S. | 10,400 | M.C. | I.S. | N.I.C. | | Good | |
| 8 | I.S. | U.C. | 9,000 | I.S. | M.C. | | N.I.C. | | Fair |
| 9 | N.P. | I.S. | 7,600 | N.P. | I.S. | A.I.Ab. | | Poor; removed | |
| 10 | M.C. | I.S. | 5,400 | M.C. | I.S. | A.I.C. | | Poor | |
| 14 | M.C. | I.S. | 8,000 | M.C. | I.S. | N.I.C. | | Good | |
| 15 | M.C. | I.S. | 7,600 | M.C. | I.S. | N.I.C. | | Fair | |
| 19 | U.C. | I.S. | 7,600 | U.C. | I.S. | A.I.C. | | Poor | |
| 21 | I.S. | N.P. | 15,000 | I.S. | N.P. | | A.I.Ab. | | Poor |
| 22 | M.C. | I.S. | 5,600 | M.C. | I.S. | N.I.C. | | Good | |
| 23 | M.C. | M.C. | 13,000 | M.C. | M.C. | N.I.C. | N.I.C. | Fair | Fair |
| 25 | M.C. | M.C. | 15,600 | M.C. | M.C. | N.I.C. | N.I.C. | Fair | Fair |
| 27 | M.C. | I.S. | 11,200 | M.C. | I.S. | N.I.C. | | Good | |
| 33 | M.C. | M.C. | 10,400 | M.C. | M.C. | N.I.C. | N.I.C. | Fair | Fair |
| 34 | M.C. | I.S. | 7,600 | M.C. | I.S. | N.I.C. | | Good | |
| 36 | M.C. | L.C. | 10,000 | L.C. | I.S. | N.I.C. | | Good | |
| 37 | M.C. | I.S. | 19,800 | M.C. | I.S. | A.I.C. | | Poor | |
| 40 | M.C. | I.S. | 1,000 | M.C. | I.S. | N.I.C. | | Good | |

A.I.Ab. indicates atrophic in abdomen; N.I.C., normal in canal; A.I.C., atrophic in canal.

## DISCUSSION

*Age of patients.* A tabulation of the age of the patients included in this study (table 2) revealed that 29 (73%) of them were between the ages of 8 and 13. Interestingly, of the patients benefitted solely by hormone therapy, 10 were in this age group, while the remaining 2 were 5 and 6 years of age, respectively. There were 8 patients younger than 8, two of whom showed complete descent, and 3 from 14 to 17 years of age, none of whom responded to treatment with pregnancy urine hormone. There were 5 patients 13 years of age, of whom only one responded to endocrine therapy. Satisfactory response to either hormonal or surgical therapy was not observed in this study in any patient 14 years of age or over.

*Spontaneous descent.* The possibility of spontaneous descent occurring at puberty has been mentioned by numerous observers. In view of the relative lack of good results from hormonal therapy in the older patients in this study, it is felt that the wisest plan of procedure is to minimize the possibility of spontaneous descent. The interests of the patients are served best by attempting to place the misplaced testicle in a normal position within the scrotum by injections of pregnancy urine hormone or by surgical fixation carried out before the ninth birthday. Should one choose to wait, some testes admittedly may descend, but the penalty for this delay may be irreparable damage to many patients.

*Incidence of hypoplasia and its relation to age of patient.* The relation of age of the patient to hypoplasia merits serious consideration. It is admitted that the only simple criteria for determining lack of development of testes are size and consistency. Conclusions as to size were reached by comparing one side with the other, or relatively established, at least, by comparing patients of the same age. A testicle was regarded as being hypoplastic when it was less than one-half the size of its mate. The normal testicle is firm and resilient, the hypoplastic testicle small, mushy and soft, often resembling a strand of tissue-like spermatic cord, epididymis or tunica vaginalis.

Among the 6 cases of bilateral cryptorchidism responding completely to hormonal therapy, there was only one patient in whom the testes were intra-abdominal (a boy 9 years of age, *case 11*). When the testes appeared in the scrotum during the course of endocrine treatment, they were considered as being normal in size and consistency. In another bilateral case in a boy of 12 (*case 18*), the testes were smaller than normal when they appeared in the scrotum. This patient has been observed for over 4 years (present age 16), and still shows definite signs of hypogenitalism. Among the 6 successfully treated cases of unilateral cryptorchidism, were two in boys of 11 years (*case 2*) and 13 years (*case 20*) in whom the undescended testicle was less than one-half the size of that of the opposite side. It would seem, therefore, that among the patients in whom complete descent occurred following endocrine therapy, were 3 instances of hypoplastic testes in boys 9, 11 and 12 years of age.

Observations regarding age and size of testes in the 20 surgically treated patients were equally informative. As already mentioned, 6 of these were bilateral at the institution of hormonal therapy. In two of them, descent of one testicle occurred following endocrine therapy, so that actually only 4 cases of bilateral and 16 of unilateral cryptorchidism were treated surgically. One instance of hypoplasia was encountered in the bilateral group (in a boy of 11, *case 6*). In the 3 remaining patients, the size and consistency of the testes appeared normal. In the unilateral cases, 5 instances of hypoplasia were encountered in boys 11, 12, 15, 16 and 17 years of age (*cases 9, 10, 19, 21, 37*). Two of these were intra-abdominal. The hypoplastic testicle was removed at operation in *case 9*. There were thus 9 patients (22.5%) who had evidence of hypoplasia after either medical, surgical, or a combination of both forms of therapy. Lack of development of the testicle was not encountered under the age of 9, but its incidence increased definitely beyond this age, thus illustrating the cost of delay.

*Reactions to injection of pregnancy urine hormone.* No serious reactions or after-effects were observed from continuous treatment with pregnancy urine hormone. After 3 months of treatment, moderate enlargement of the penis and scrotum was observed in most instances. When continued for more than 4 months, priapism was often noted. With cessation of treatment, the size of the genitalia returned to approximately that before the institution of therapy, and priapism disappeared. Many patients complained of pain at the site of injection. Small areas of local reaction were encountered frequently, but these usually became less severe after treatment had been in progress for several weeks. One boy of 6 with unilateral cryptorchidism showed extreme reactions consisting of intense redness and swelling of the entire arm, and fever of 104° following each injection. Another bottle of pregnancy urine hormone from the same company, as well as still another prepared by a second company gave similar reactions. In this patient, it was felt inadvisable to continue endocrine therapy. Later he was successfully treated by surgery.

The use of male sex hormone in the treatment of cryptorchidism has been advocated recently by such investigators as Zelson and Steinitz (7). Moore and Price (8) have demonstrated that crystalline androsterone, testosterone, and testosterone pripionate produced gross decrease in the size of the testes, reduction in size of the tubules, sloughing of cells into the lumen and delay in development of complete spermatogenesis. These findings were confirmed subsequently by Sainton et al. (9), Biddulph (10), and by Greene and Burrill (11) although the latter investigators believe that the inhibitory effect of androgenic substances on immature testes is only temporary. In view of these significant findings, it was deemed inadvisable to use male sex hormone in any of the patients reported in this communication.

*Dosage, length of treatment.* Pregnancy urine hormone was administered 3 times weekly. There seemed to be no advantage in administering it more frequently. Early in the course of treatment, most patients would have objected strenuously to more frequent administration. In all instances except 3, a dose of 200 R.U. per injection was maintained. In these 3, doses of 200 U were given for from 6 to 8 weeks. Observing no change in the position of the testes, it was increased to 500 U per injection with no enhancement in efficacy of treatment. The results observed in these 3 cases seem to indicate that there is no advantage in administering the hormone in larger amounts or more frequently.

To continue treatment beyond 4 months is generally a waste of time and hormone. Treatment was continued for 5 months or longer in 11 patients. In one of these, a case of bilateral cryptorchidism, unilateral descent occurred, while the others showed no change following such prolonged periods of treatment. In one boy of 5, 102 injections were administered without correction of the cryptorchidism. The earliest time in which descent was observed was 4 weeks, the latest 4 months. Because of these results, it appears that there is no advantage in continuing hormonal therapy beyond 4 months. Failing to secure satisfactory testicular descent after a 4-month course of pregnancy urine hormone, it becomes necessary to resort to surgery. This is best done before the age of 9.

*End results of hormonal, surgical, or combined hormonal and surgical treatment of cryptorchidism.* The results obtained from endocrine therapy alone or from

endocrine therapy followed by surgery reveal that neither type of therapy is the final answer, in the treatment of cryptorchidism. As has already been shown, complete descent was obtained in 12 cases or 30% from simple hormonal therapy, and an additional 8 cases or 20% responded to surgery, a grand total of 20 or 50%. Because of the extreme youth of one patient, and because permission for operation could not be obtained in 7 others, treatment was not completed in 8 or 20%, leaving 30% who received only partial or no benefit at all from treatment. Analysis of the status of this group showed the existence of one or more of the following conditions: (*a*) lack of development of one or both testes, (*b*) position of testicle unchanged, (*c*) retraction of testicle high into the scrotum or back into the canal following surgery. The presence of these conditions in approximately one-third of the patients lends support to the belief that the ultimate in the treatment of cryptorchidism is yet to be attained.

Many of these patients showed abnormalities of personality. Realizing their deficiencies, they often develop defense reactions. Thus one of them is insulting, blustering, offensive, and lacking in regard for the rights of others. In aggressive attempts to see one of us, he has incurred the ill-feeling of the secretary and one of the associates in our clinic—to the point that they do not care to have further dealings with him. In another boy who has been observed for 6 years, testicular descent and development have been highly successful. This patient, however, has not been rehabilitated completely. He is not yet "one of the boys," and definitely lacks the initiative so essential to good personality and accomplishment. Still another boy who has been observed for 5 years, exhibits marked peculiarities of personality. He does not mix with other boys, he goes and comes by himself, and has not a friend in the world. He is moody, critical, disagreeable and impertinent. He lacks initiative, has no outlets, and takes part in none of the sports or games of boys his age. He lacks self-control. Recently, on slight provocation arising in a restaurant, he hit another boy in the face with a piece of pie, and more recently in a rage he attempted to strangle his mother. Other instances of personality changes could be cited, but those described above suffice to illustrate the serious nature of these changes, as well as to emphasize the importance of affecting adjustments through proper psychologic guidance.

What has been considered success heretofore in the treatment of cryptorchidism, perhaps is success in a limited way only. Complete rehabilitation must encompass more than testicular descent. In some cases in which a satisfactory position of the testes was obtained by therapy, the degree of development, the size of the genitals and the development of secondary sex characteristics was retarded, or marked personality changes were noted. Several cases of hypogenitalism were encountered, making it vital in these patients to continue some form of therapy in an effort to approximate normal genital development. Thus, even after satisfactory descent has been achieved, the physician's duty to his patient is not ended until as complete a development of both primary and secondary sexual characteristics as it is possible, has been obtained, and until the proper psychologic adjustments have been made.

From our study have arisen a number of questions which must remain unanswered until further investigation furnishes additional information of a fundamental nature. It should be pointed out that the present communication, as well as many others, have dealt with the problem of cryptorchidism from two points of view: (*a*) anatomical restitution of the affected organs to a normal position within the scrotum, and (*b*) insurance of proper development. Both are of immediate concern to the physician, and the available answers are satisfactory. Of equal importance, but remaining unanswered, are the questions concerned with the future of the patient: (*a*) what will be the functional result as it pertains to fertility and the elaboration of male sex hormone, and (*b*) what is the possibility of degenerative and malignant changes? These questions must await reports a decade or more hence for final answers. It must be determined why degenerative changes are so frequent in the undescended testicle. Since spermatogenesis is a continuous process, why is it not possible to induce restoration of function after atrophy has occurred in the human testes just as seems to be the case in the rat? In cryptorchidism, has there been some serious irremedial break in early development, or are certain types of cells destroyed beyond repair? Are other hormones in addition to the pituitary gonadotropic hormone concerned in development? Investigations along these lines should yield information of definite value in a better understanding of cryptorchidism.

SUMMARY

In 40 cases of cryptorchidism selected under the strictest criteria and treated with pregnancy urine hormone, complete descent occurred in 12 instances (30%).

With surgical fixation of the testicle, undertaken in 20 of the 28 cases in whom hormonal therapy failed, complete descent occurred in an additional 8 patients (20%).

Complete descent from hormonal therapy alone, or from a combination of hormonal management and surgical fixation was obtained in a total of 20 patients or 50%.

The use of potent preparations of pregnancy urine

in the treatment of cryptorchidism is advisable. A course of treatment consists in the administration of 200 R.U. of such a preparation 3 times weekly until a total of 7,000 to 10,000 U have been given over a period of 3 to 4 months. If satisfactory results have not been obtained after such a course of therapy, the patient should be referred to a competent surgeon for correction of the anomaly.

In all, 9 instances of lack of development of the testicle were observed after either medical, surgical, or a combination of both forms of therapy. Hypoplasia was not encountered before the age of 9, but its incidence increased definitely beyond this age. Thus age assumes great significance relative to the time element in the treatment of cryptorchidism.

While it must be admitted that spontaneous descent does occur in some instances after puberty, it would appear that in the best interests of the patient, this possibility should be minimized, and that the treatment be carried out before the ninth birthday with pregnancy urine hormone, and if this proves unsuccessful, with surgical fixation of the misplaced testicle in the scrotum. Only by adopting such a policy can the dangers of irreparable hypoplasia of the testicle be eliminated to a large extent.

Personality changes may occur in the victim of cryptorchidism and persist despite induced descent. Complete success in the management of cryptorchidism demands restitution of the affected organs to a normal position in the scrotum, normal development of the primary and secondary sexual characteristics, and proper psychologic guidance for those patients who manifest serious changes in personality.

Pregnancy urine hormone, in the form of Antuitrin-S, was supplied by Parke, Davis & Co., Detroit, Mich., and in the form of Korotrin, by the Department of Medical Research, Winthrop Chemical Company, New York City.

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# Methyl Testosterone IV. Observations on the Hypermetabolism Induced by Methyl Testosterone[1]

[Testosterone and Metabolism]

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A RISE IN THE BASAL METABOLIC RATE has been reported to occur in human subjects receiving testosterone propionate by Kenyon et al. (1, 2, 3), Thompson and Heckel (4), and Eidelsberg and Ornstein (5). Kochakian and Murlin found a slight increase in energy metabolism of a castrated dog treated with testosterone propionate (6), but failed to corroborate this in subsequent studies (7, 8). McCullagh (9), Byron and Katzen (10), and McCullagh and Rossmiller (11) found an increase to occur in the B.M.R. of patients receiving methyl testosterone orally. The 10 patients studied by McCullagh and Rossmiller (11) showed increases in B.M.R. ranging from 12 to 54% of normal. This paper deals with additional studies on 5 of these patients, and on 6 others in whom a similar metabolic increase was induced by methyl testosterone. Studies have been made, with and without therapy, on the blood cholesterol, blood iodine, respiratory quotient, circulation time, the nitrogen balance and urinary excretion of various electrolytes.

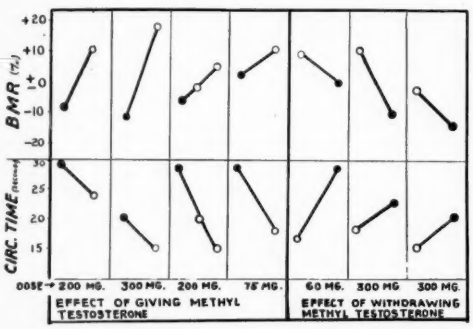


Fig. 1. Circulation time and B.M.R. in relation to methyl testosterone.

## MATERIAL AND METHODS

Our cases include 9 of eunuchoidism, 1 pituitary dwarf and 1 normal individual. Of the eunuchoids, 5 exhibited testicular atrophy of unknown etiology; 1 had mumps prepuberally with subsequent testicular atrophy; 2 had bilateral orchidopexies early in puberty with subsequent atrophy; and one had a suprasellar tumor as indicated by suprasellar calcification in the skull roentgenogram. All patients, except the one normal individual, had marked or total deficiency of sexual maturation. *Cases 1* to *4* had a considerable degree of maturation produced by long-continued testosterone propionate therapy before our present studies were begun. *Cases 5, 6* and *10* had not had long periods of androgen therapy, but had matured to varying degrees under testosterone propionate treatment. The other cases were studied from the beginning of androgen therapy. Periods of observation were from 3 to 7 months in length.

All of the patients received methyl testosterone[2] orally in doses varying from 50 mg. to 300 mg. daily, except for one course of 500 mg. daily for 10 days (*case 2*). *Cases 2* and *8* also received some testosterone propionate therapy during the period of study (fig. 2). In each case observations were made during therapy, and either before therapy or some time after withdrawal. Most of the patients were ambulatory

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[1] Read before the twenty-fifth annual meeting of the Association for the Study of Internal Secretions May 3, 1941 at Atlantic City, N. J.

[2] The methyl testosterone (Oreton-M) and testosterone propionate (Oreton) were made available through the kindness of Dr. Erwin Schwenk and Dr. Max Gilbert of Schering Corporation, Bloomfield, N. J.

and pursued their usual occupations. The ages range from 19 to 35 years. The heights were within normal limits except for *case 10*, the pituitary dwarf; the weights were within normal range except for *case 2*, in which the patient was about 20 pounds overweight. None of the cases showed any clinical evidence of hypothyroidism.

All tests were made with the patients fasting. Determinations of basal metabolic rates were made with Sanborn Grafic machines; the Mayo Clinic tables were used. Each test represents two runs.

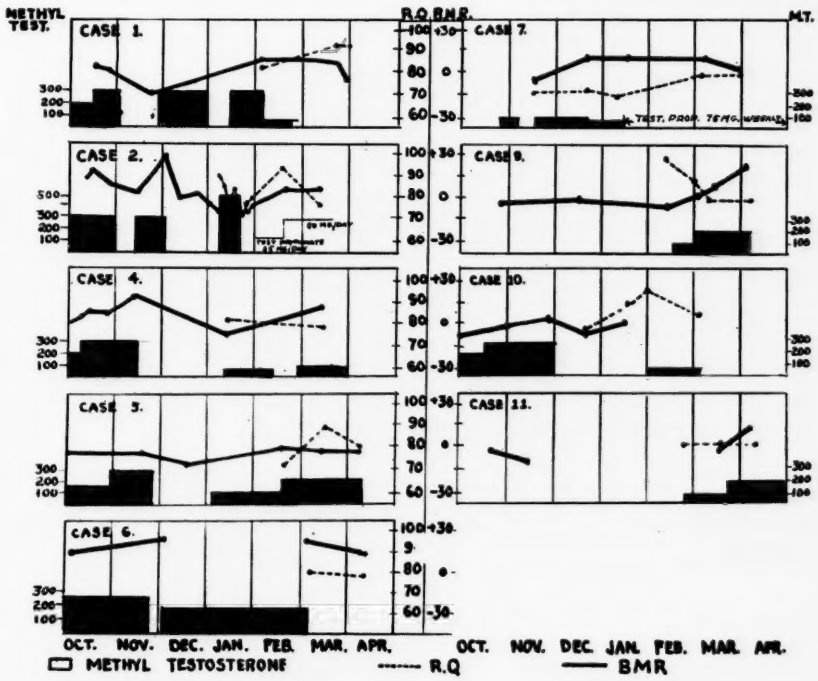


Fig. 2. Respiratory quotient in relation to methyl testosterone therapy and B.M.R.

Blood cholesterol estimations were made by Sackett's modification of Bloor's method (12). Blood iodine was determined by the method of McCullagh (13). Respiratory quotients were determined by the method described by Peters and Van Slyke (14), using a Tissot spirometer; the patients were prepared as for a basal metabolism determination. Circulation time was determined by the taste perception method, using 20% sodium dehydrocholate (Decholin), with the patient in the recumbent position. The same arm was always used in each patient, and each test is the average of two or three determinations from as many timed injections of 3 to 5 cc. each.

There were certain differences in the methods of making the studies of nitrogen, fluid and electrolyte balance. *Case 4* (fig. 4) was hospitalized in July, and remained inactive although ambulatory. He ate a fixed diet for 13 days, throughout which urine excretion studies were made; during the last 7 days he received 200 mg. of methyl testosterone daily. His diet consisted of: carbohydrate, 167 gm.; fat, 100 gm.; protein 50 gm.; total calories 1,768. This diet contained 2.05 gm. sodium, 1.7 gm. potassium, 3.0 gm. chloride, and 8 gm. of nitrogen. Each portion was weighed on balance scales to the tenth of a gram. The total daily fluid intake, including that in the diet, averaged 2,400 cc., but varied from this by as much as 200 cc.

*Case 2* (fig. 3) resided in the hospital during his period of study, which was in January, but went out to work each weekday. He ate his fixed diet for 6 days before excretion measurements were begun. From the 9th to 18th days, inclusive, of the 26-day period of balance studies, he received 500 mg. of methyl testosterone daily. His diet contained 233.5 gm. of carbohydrate, 127.7 gm. of fat, and 77.5 gm. of protein, the total caloric value being 2,393. The sodium content was 3.76 gm., potassium 5.57 gm., calcium 1.19 gm., phosphorus 2.06 gm., nitrogen 12.4 gm., and chloride 5.41 gm. Portions were weighed on balance scales to the tenth of a gram. The total fluids, including those in the diet, were 3,000 cc.

*Case 9* (fig. 5) differed from the others in that his studies began in April after he had taken 200 mg. of methyl testosterone daily for 2 months, and treatment was stopped

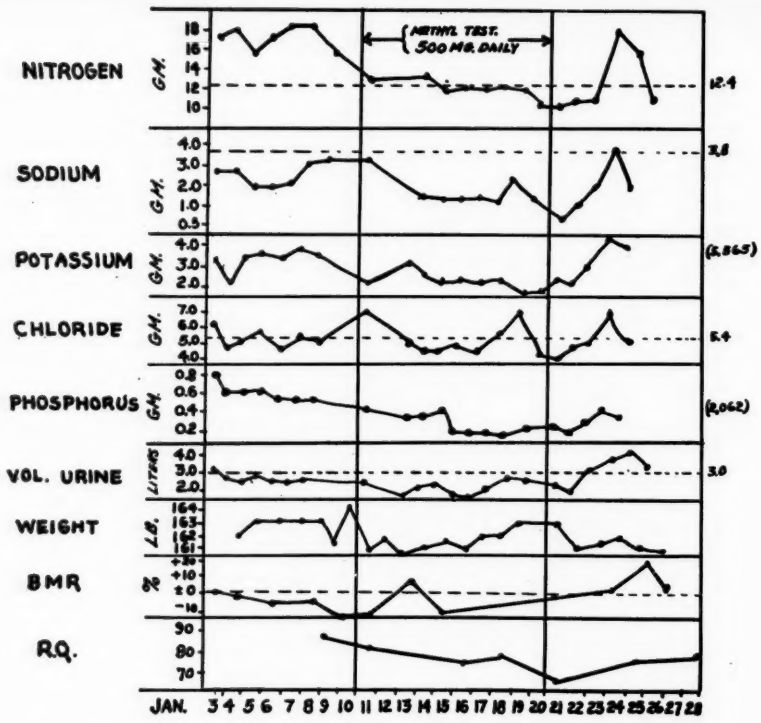


Fig. 3. *Case 2*, eunuchoid; excretion levels of urinary elements in relation to B.M.R. and R.Q.

during the period of balance study. He ate his fixed diet for 5 days before excretion measurements were begun. The diet was prepared at home, and was weighed on spring scales such as are ordinarily used by diabetic patients. Methyl testosterone was discontinued after 6 days of the 11-day period of balance study. The diet consisted of 263 gm. of carbohydrate, 158.5 gm. of fat, and 79.2 gm. of protein, a total caloric content of 2,795. The

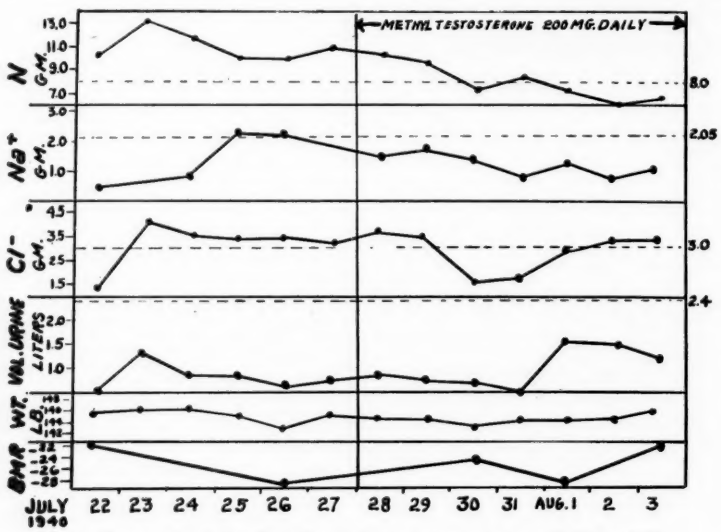


Fig. 4. *Case 4*, eunuchoid; effect of methyl testosterone on urinary N, Na, and Cl.

amount of sodium was 5.30 gm., potassium 4.17 gm., nitrogen 12.6 gm., and chloride 8.45 gm. The total daily fluid intake was 2,450 cc.

The food was not chemically analyzed, but all portions were weighed as described and each patient ate the same foods each day of his period of study. All fluids were measured accurately, and exact 24-hour specimens of urine were collected. All the specimens were analyzed by the same technician. The patients had been under observation for considerable periods, and were schooled in cooperation.

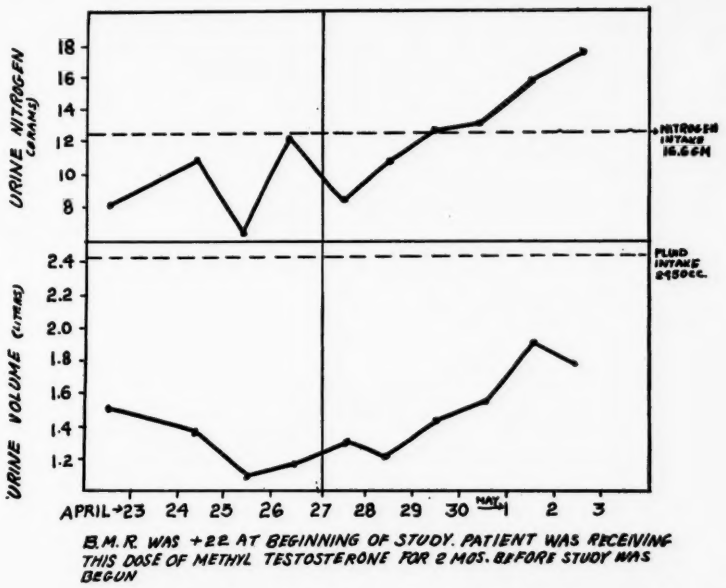


Fig. 5. *Case* 9, eunuchoid; effect of methyl testosterone on urinary nitrogen.

## RESULTS

1. *Hypermetabolism.* The average rise in the B.M.R. in each patient on each of the various doses of methyl testosterone is shown in table 1. Each figure in the table represents two or more consistent determinations on different dates.[3]

Comparison of average increases in B.M.R. on increasing doses of methyl testosterone for the individual patient is possible in 9 of the 13 cases. It is not clearly evident from these to what extent the rise in B.M.R. parallels the dose of methyl testosterone; however, the figures suggest that the rate of increase in B.M.R. becomes less as a dose of 300 mg. daily is approached.

Average increases in B.M.R. for the whole group were 15% of normal B.M.R. on 100 mg. per day, 24% on 200 mg. per day, and 26% on 300 mg. per day. However, the degree of response varied greatly among the patients.

Increase in sympatomatic response was not noted by the patients when the daily dose was raised from 100 mg. to 300 mg., with the exception of *case* 5.

The physical effects of methyl testosterone, androgenic and otherwise, have been reported previously (15). These include increased activity, a thickening of the skin with increased oiliness and smoothness, increase in muscle bulk in some patients, and weight gain. There was no consistent change in pulse rate or blood pressure. We particularly noted that our

TABLE 1. EFFECT OF METHYL TESTOSTERONE UPON B.M.R.

| Dose | 0 | 100 mg. | | 200 mg. | | 300 mg. | |
|---|---|---|---|---|---|---|---|
| Case | Av. B.M.R. | Av. B.M.R. | Increase % | Av. B.M.R. | Increase % | Av. B.M.R. | Increase % |
| 1. Eunuchoid | −20 | − 7 | 13 | ± 0 | 20 | + 3 | 23 |
| 2. Eunuchoid | −12 | +15 | 27 | +28 | 40 | +28 | 40 |
| 3. Eunuchoid | −20 | − 7 | 13 | | | | |
| 4. Eunuchoid | −24 | | | + 8 | 32 | +21 | 45 |
| 5. Eunuchoid | −23 | − 3 | 20 | − 3 | 20 | − 3 | 20 |
| 6. Eunuchoid | − 6 | +13 | 19 | +22 | 28 | | |
| 8. Eunuchoid | −13 | + 2 | 15 | | | | |
| 9. Eunuchoid | − 7 | ± 0 | 7 | +20 | 27 | | |
| 10. Pituitary Dwarf | −13 | | | − 3 | 10 | − 3 | 10 |
| 11. Normal | −11 | − 4 | 7 | +14 | 25 | | |
| 12. Eunuchoid | −17 | − 2 | 15 | | | | |
| 13. Heart Disease | −20 | | | − 2 | 18 | + 1 | 21 |
| Average | −15 | + 1 | 15 | + 8 | 24 | + 9 | 26 |

All values are percentages of normal B.M.R.

[3] Results on 2 patients, 1 with eunuchoidism and 1 with functional impotence are included in table 1, but these were not studied otherwise (*cases* 12 and 13).

patients did not experience palpitation, increased sweating, dyspnea, insomnia, or inability to rest; nor was there evidence of cardiac overactivity, despite the change in circulation time. They exhibited no signs suggesting a striking increase in energy, nor did they show evidence of the restlessness common in hyperthyroidism.

TABLE 2. BLOOD CHOLESTEROL IN RELATION TO B.M.R.

| B.M.R. | (−28 to −11) | (−10 to −1) | (+1 to +10) | (+16 to +30) |
|---|---|---|---|---|
| | 132 | 165 | 141 | 275 |
| | 116 | 167 | 152 | 224 |
| | 176 | 176 | 171 | 156 |
| | 176 | 150 | 200 | 213 |
| | 197 | 160 | 142 | 292 |
| | 217 | 159 | 138 | |
| | 143 | 134 | 155 | |
| | | 166 | 145 | |
| | | 189 | 152 | |
| | | | 250 | |
| | | | 154 | |
| | | | 230 | |
| Average | 166 | 162 | 164 | 232 |

Blood cholesterol values are mg./100 cc. of blood.

2. *Blood cholesterol.* We previously observed that an increase of blood cholesterol above levels considered normal sometimes occurred while the patient was taking methyl testosterone. Serial determinations in these cases have shown that the blood cholesterol tends to follow a curve parallel to that of the B.M.R. in only a minority of cases. Therefore the results,

TABLE 3. BLOOD CHOLESTEROL IN RELATION TO METHYL TESTOSTERONE THERAPY

| No therapy | 50 mg. daily | 100 mg. daily | 200 mg. daily | 300 mg. daily |
|---|---|---|---|---|
| 132 | 194 | 152 | 154 | 275 |
| 141 | 145 | 165 | 152 | 250 |
| 150 | 160 | 167 | 224 | 166 |
| 156 | 197 | 214 | 169 | 161 |
| 116 | | 159 | | 178 |
| 160 | | 189 | | 213 |
| 168 | | 142 | | 292 |
| 176 | | 138 | | 219 |
| 179 | | | | 200 |
| 134 | | | | 265 |
| 176 | | | | 207 |
| 171 | | | | |
| 176 | | | | |
| 190 | | | | |
| 217 | | | | |
| 143 | | | | |
| Average 162 | 174 | 166 | 175 | 216 |

totaling 43 determinations, have been compiled and are presented in tables 2 and 3, showing the relation of blood cholesterol in the series as a whole to B.M.R. and to intensity of methyl testosterone therapy.[4]

[4] A series of fasting blood cholesterol determinations on 25 patients having B.M.R. determinations of −10 to +10% and no evidence of metabolic disease, gave a mean blood cholesterol level of 166 mg.% with a range of values from 130 to 220 mg.%.

The average blood cholesterol level with basal metabolic rates of −28 to −11% was 166 mg.%; the average level with rates of −10 to −1 was 162 mg.%; the average with rates of +1 to +10 was 164 mg.%; and the average with rates of +16 to +27 was 232 mg.% (table 2). Similarly, the average of all determinations at any level of methyl testosterone therapy varies little until the 300 mg. dose is reached, when the figure is distinctly higher (table 3).

The 11 cholesterol levels of 200 or above were distributed among 6 cases. Ten determinations were made during treatment. The other (217 mg.%) was made one month after discontinuing the largest dose per kilogram given. During this preceding period of treatment the blood cholesterol level had been 265 mg.% (*case* 10).

TABLE 4. BLOOD IODINE IN RELATION TO B.M.R.

| B.M.R. | (−20 to −10) | (−10 to 0) | (0 to +10) | (+10 to +20) | (+20 to +30) |
|---|---|---|---|---|---|
| *Case* | | | | | |
| 1 | | | 8.0 | | |
| 1 | | | 9.1 | | |
| 2 | | 3.8 | 10.7 | | 3.0 |
| 2 | | 4.4 | 7.8 | | 8.6 |
| 2 | | | 5.5 | | |
| 4 | | 9.9 | | | |
| 5 | 6.9 | 5.2 | | | |
| 6 | | | | 8.4 | 14.0 |
| 6 | | | | | 11.4 |
| 7 | | 15.2 | 8.7 | | |
| 7 | | | 7.4 | | |
| 8 | | | 12.7 | | |
| 8 | | | 10.2 | | |
| 9 | 6.2 | 5.2 | | | |
| 10 | 5.8 | 12.8 | | | |
| 11 | 15.2 | | | | |

3. *Blood iodine.* In 25 determinations of the blood iodine level there was a considerable range of variation, from 3.0 to 15.2 gamma % (table 4). None of the figures significantly exceeds normal range. No correlation could be found between blood iodine level and B.M.R.; nor could any be found between blood iodine level and intensity of methyl testosterone therapy.

4. *Circulation time.* The velocity of blood flow showed a consistent alteration in the 7 cases in which it was measured (fig. 1). The velocity increased with methyl testosterone therapy, or decreased upon withdrawal; accordingly it varied with the B.M.R. as shown in figure 1. Since the method is of limited accuracy, no cognizance is taken of the amount of change indicated by the figures, except in *case* 9, in which the striking progressive change from 27 seconds to 19 seconds to 16 seconds in four weeks of therapy is worthy of mention.

5. *Respiratory quotient.* The respiratory quotient results in relation to methyl testosterone therapy and B.M.R. are shown in graphic form in figure 2. The results show a downward trend in R.Q. on therapy, or an upward trend upon withdrawal of therapy in 5 cases; both occurred in *cases 2* and *10*. No significant shift in R.Q. was noted in 4 cases, and in *case 5* the R.Q. fluctuated widely without explanation.

Changes were particularly striking in *case 2*, in which the R.Q. fell from 0.86 to 0.69 during 10 days with 500 mg. of methyl testosterone daily, while the nitrogen excretion on a fixed dietary intake fell sharply and the B.M.R. showed no more than a beginning rise during the same period (fig. 3). The R.Q. in *case 9* also showed a well-marked, progressive fall on therapy, from 0.93 to 0.80 in four weeks, while the rise in B.M.R. lagged behind, as in *case 2*. A lag in the fall of B.M.R. behind the rise in R.Q. on withdrawal of methyl testosterone therapy is suggested in *cases 1* and *7*.

Notable but not corresponding to the other cases in time relationships, there being a much slower shift, was the marked rise in R.Q. in *case 10*, which occurred gradually over a two-month period following cessation of methyl testosterone therapy. This patient was a pituitary dwarf who weighed about 82 pounds. He had received 300 mg. of methyl testosterone daily for 6 weeks. This is twice the dose per kilogram of body weight given to any other patient in this series for a comparable period. The results, in conjunction with the delayed fall in blood cholesterol mentioned above, suggest that prolonged retention of the hormone may have occurred. This hypothesis is in some degree supported by the fact that methyl testosterone is not excreted in the urine in quantities measurable by capon comb-growth or colorimetric determination (16). If methyl testosterone must be altered before it can be excreted, there may be a significant limit to the rate at which the body can do this.

6. *Nitrogen, electrolyte and fluid balance. Case 4* (fig. 4) did not establish an exact balance before urine excretion measurements were begun, but upon beginning methyl testosterone therapy, showed a steady decline in excretion of nitrogen and sodium over the 7 days. Chloride excretion fell sharply below intake on the fourth and fifth days of treatment, and then rose again to the pretreatment level. The urine volume increased considerably in the last 3 days of therapy; this may have been caused by a change to cooler weather. There was no significant change in his weight or B.M.R. throughout the period of study. Subsequently a hypermetabolism occurred.

*Case 2* (fig. 3) showed a well-marked decline in the excretion of nitrogen, sodium, potassium, phosphorus and water during the period of methyl testosterone therapy, with a sharp rise in the excretion of these substances after cessation of therapy, reaching a peak on the fourth day, except that the peak of water excretion was reached on the fifth day. No change in chloride excretion occurred unless a one-day lag in the establishment of the effects of beginning and discontinuing methyl testosterone therapy is assumed, in which case the daily chloride excretion during the period of methyl testosterone effect was 0.4 gm. less than the rest of the time. The patient lost 6 pounds in weight during the week prior to balance studies, but no significant change occurred in weight or B.M.R. during the studies.

*Case 9* had a basal metabolic rate of +22% just before balance studies were begun. His non-treatment B.M.R. had been about −6%. Nitrogen retention is indicated during the period of continuance of methyl testosterone therapy which he had been receiving continuously for two months before balance studies were begun. Upon withdrawal of the hormone, the nitrogen excretion rose well above the intake level and the water excretion also showed a sharp rise. Two weeks after the withdrawal of therapy his B.M.R. had fallen to −4%.

These measurements indicate an average daily nitrogen retention under the influence of methyl testosterone of 0.7 gm. for *case 4* and *case 2*, and 2.64 gm. for *case 9*. Figures are not corrected for fecal nitrogen. It seems unlikely that fecal nitrogen measurements would cancel the large positive balance in *case 9*; however, it must be remembered that his diet was not weighed as accurately as that of the others.

## DISCUSSION

The raising of the B.M.R. in these cases by 10 to 45% of normal (11 to 60% of the pretreatment level) by methyl testosterone may conceivably be brought about by a direct tissue effect, or intermediately through some other gland. Such direct tissue effects are known to occur with thyroxine and other thyroid preparations, and with various toxic agents. Other possible modes of action include stimulation of: *a*), the pituitary gland, with the production of a specific metabolic hormone or the thyrotropic hormone; *b*), the thyroid gland; *c*), the adrenal medulla; and *d*), possibly some other glandular organ or system.

In view of the depression of the production of gonadotropic hormone by the pituitary which accompanies the administration of androgens, it may be doubted whether methyl testosterone exerts any stimulating effect upon this gland.

The absence of increased sweating, tremor, tachycardia, and blood pressure rise in these patients suggests that the adrenal medulla is not acted upon to produce a hypermetabolism.

No untoward reactions have occurred with methyl testosterone to suggest that its effect is toxic. The only untoward clinical effect of any sort was the production of an undesirable degree of edema in one patient. However, methyl testosterone has the property of decreasing tolerance to glucose (17), which suggests the possibility of a toxic action upon the liver.

This leaves for the present consideration the possibilities that the metabolic effect is directly upon the thyroid gland, stimulating it to increased secretory activity, or directly upon tissues. We have analyzed our results with a view to determining whether the hypermetabolism induced by methyl testosterone is physiologically like that induced by thyroid hormone.

The increase in velocity of blood flow is for this purpose only a corroboration of the presence of an increased basal metabolism. It has also been observed in all these cases, that the level of red corpuscles and hemoglobin in the blood has been either maintained or increased with methyl testosterone therapy (17), so that the increase in velocity of blood flow has not been offset by any decrease in oxygen-carrying capacity.

Carriere et al. (18) and Nathanson et al. (19) have separately demonstrated histologic changes in the thyroid glands of animals injected with testosterone propionate, which suggest that a hypersecretion occurred from these thyroids. The changes noted include increase in cell height, increase in number of mitotic figures, assumption of a round shape by the nucleus, migration of the nucleus toward the base of the cell, and vacuolization of the colloid. No metabolic studies on the animals so injected were reported.

The time required to produce a rise in B.M.R. with methyl testosterone, and the time required for the rise to disappear after withdrawal of therapy, vary considerably in each patient. The rise in particular appears slower than that which would be expected from thyroid administration. In our experience, the rise in basal metabolism with a fixed dose of methyl testosterone begins within 8 to 14 days, but may take as long as two months to attain its maximum; while the regression to the pretreatment level on withdrawal of therapy may occur within two weeks to three months, usually nearer the latter. The rise in B.M.R. produced by thyroid preparations usually is complete within 8 to 10 days, a shorter time than the average observed in our cases with methyl testosterone; the fall to pretreatment level after withdrawal of thyroid hormone requires about two months for a myxedematous individual (20), and probably less time for a normal one in whom a hypermetabolism is produced.

Of a total of 44 blood cholesterol determinations, 12 were above 200 mg.%. Of these, 6 were above 220 mg.%, the elevation being apparently caused by methyl testosterone. This is of significance in view of the fact that the blood cholesterol level is nearly always average normal or less in hyperthyroidism. Our findings do not indicate that methyl testosterone has a consistent tendency to elevate the blood cholesterol, but show only that an elevated blood cholesterol and a hypermetabolism may occur concomitantly under the influence of methyl testosterone.

The blood iodine results show no consistent relationship of blood iodine level either to methyl testosterone therapy or to the B.M.R. in the individual cases or in the group as a whole. We desire to point out, therefore, that none of the determinations significantly exceed normal limits, and accordingly there is no evidence of hyperthyroidism in them.

The nitrogen balance studies in *cases 2* and *4* (fig. 3 and 4) were terminated prior to the occurrence of a demonstrable rise in B.M.R. The periods of observation on therapy were 8 days for *case 4* and 10 days for *case 2*. *Case 4* continued his treatment and later exhibited a hypermetabolism. The tendency in these cases to a retention of nitrogen, potassium, phosphorus, sodium, possibly chloride, and water while under therapy, together with the rapid excretion of these elements shortly following withdrawal of the hormone, is in keeping with the findings of Kenyon et al. (1, 2, 3), and McCullagh and McGurl (22) who employed testosterone propionate, and those of Thorn and Engel (21) who used testosterone propionate and certain other steroids. Methyl testosterone therefore resembles testosterone propionate in causing retention of these substances. Furthermore, it is probably capable of causing nitrogen retention in the presence of an induced hypermetabolism. The B.M.R. in *case 9* had risen to +22% under therapy (200 mg. daily) when measurements of urinary nitrogen excretion on a fixed diet were begun (fig. 5) Urinary nitrogen excretion averaged 2.64 gm. below intake per day until methyl testosterone was withdrawn, when it quickly rose above the intake level. This patient also showed a measurable increase in muscle bulk during the same period of treatment.

Measurements of non-protein nitrogen were not made in our cases but serial estimations of blood urea in several cases showed levels which were within normal range and did not indicate any tendency to rise or fall with methyl testosterone therapy.

It has been shown by Byrom (23) that the normal individual as well as the myxedematous one when given thyroid hormone shows an increased output of nitrogen, sodium, potassium, and chloride as well as an increased output of urine, all of which are opposed to the effects here observed with methyl testosterone.

In summarizing the clinical and laboratory observations, therefore, there is considerable evidence that

methyl testosterone does not produce a rise in B.M.R. by a thyrotropic action, nor does it have a thyroid-like effect upon the tissues.

We feel that the changes in respiratory quotient, although observed in only a part of the cases, probably indicate that the R.Q. tends to fall with methyl testosterone therapy and rise with its withdrawal, inasmuch as the most accurate and complete studies are included among the 5 cases in which this change was shown. The most likely explanation of the shift in respiratory quotient would appear to be that it is due to increased oxidation of fat, with or without decreased oxidation of glucose. That the latter effect may occur is suggested by the well-marked decrease in glucose tolerance in several of these patients when given methyl testosterone (17). There also may be some degree of gluconeogenesis from fat or protein. In *cases 1, 2, 7* and 9 there appears to be a lag in the change of B.M.R. behind the change in respiratory quotient. If this lag is real, and it probably is, it is possible that both increased oxidation of fat and decreased oxidation of glucose may occur soon after therapy is begun, and the increased oxidation of fat may become relatively greater as treatment continues.

## SUMMARY AND CONCLUSIONS

Of 11 patients studied, methyl testosterone produced a rise in B.M.R. in all. The degree of rise varied much among the patients. Four developed hypermetabolism.

The velocity of blood flow increased or decreased as the basal metabolic rate rose or fell, respectively, under the influence of methyl testosterone.

Blood cholesterol levels in excess of 220 mg.% occurred in the presence of a hypermetabolism in 4 patients.

No significant rise in blood iodine above the normal range has followed the feeding of methyl testosterone.

In 10 cases studied, the basal R.Q. fell with methyl testosterone administration or rose with its withdrawal in five; in four no significant change occurred, and in one there was an unexplained shift. The occurrence of these changes in R.Q. with the changes noted in B.M.R. suggest that increased oxidation of fat is a metabolic effect of this hormone.

The hormone is shown to share with testosterone propionate the property of causing nitrogen, electrolyte and water retention. In one case nitrogen retention appears to have occurred in the presence of a hypermetabolism induced by the hormone.

From the results obtained in this study, and from clinical observations, it appears that the metabolic effects of methyl testosterone differ in important respects from those of thyroid hormone; and it is suggested that the two hormones may produce hypermetabolism by basically different mechanisms.

Our thanks are due to Miss Muriel Thompson, Mr. Ross Guillet and Miss Elsie Russ for valuable technical assistance.

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# The Effect of Female Sex Hormone upon the Volume of Seminal Fluid in Man

[Seminal Fluid Volume]

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THE EFFECT OF an estrogenic substance, alpha-estradiol benzoate, upon the volume of the seminal fluid was studied in five men.

The alpha-estradiol benzoate[1] was given by intramuscular injection in doses which varied from 6,000 to 12,000 R.U. 3 to 6 times a week. Table 1 shows the number of patients, specimens examined, and the volume of seminal fluid obtained before, during and after treatment, also the total amount of alpha-estradiol benzoate injected and the number of injections given during each period. Figures 1, 2, 3, 4 and 5 were prepared from the data in the table and they illustrate the changes in the volume of the seminal fluid.

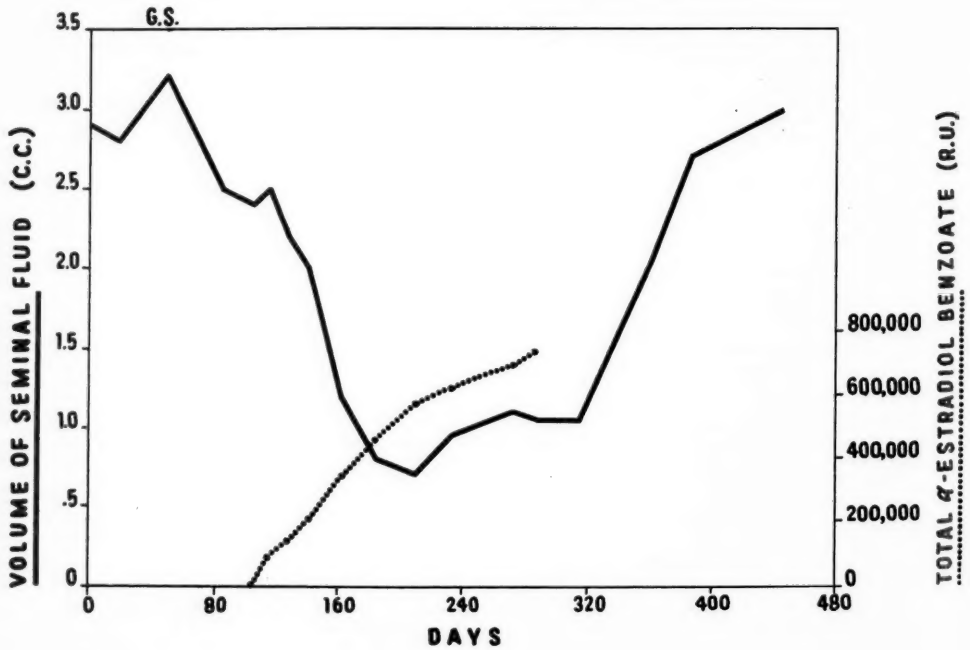


Fig. 1

*Method of Examination.* The semen was obtained by having the patient ejaculate directly into a wide mouth, small glass container. The specimen was measured in a graduate cylinder calibrated to 0.1 cc.

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[1] The Alpha-estradiol benzoate under the trade name "Progynon-B" was generously supplied by Schering Corp., Bloomfield, N. J.

TABLE 1. RELATIONSHIP OF VOLUME OF SEMINAL FLUID TO INJECTIONS OF ALPHA ESTRADIOL BENZOATE IN THE HUMAN MALE

| Patient and age | Volume of seminal fluid | | Time specimen obtained | | Treatment | |
|---|---|---|---|---|---|---|
| | before treatment | during and after treatment | after treatment began | after treatment stopped | total amount alpha-estradiol benzoate injected | number of injections during period before collection of semen |
| | cc. | cc. | days | days | R.U. | |
| G.S., 72 | 2.9 | 2.50 | 11 | | 100,000 | 10 |
| | 2.8 | 2.20 | 23 | | 148,000 | 9 |
| | 3.2 | 2.00 | 37 | | 210,000 | 8 |
| | 2.5 | 1.20 | 57 | | 340,000 | 13 |
| | 2.4 | 0.80 | 80 | | 460,000 | 12 |
| | | 0.70 | 105 | | 570,000 | 14 |
| | | 0.95 | 129 | | 631,000 | 13 |
| | | 1.10 | 167 | | 695,000 | 16 |
| | | 1.05 | 182 | | 743,000 | 8 |
| | | 1.05 | | 28 | | |
| | | 2.00 | | 73 | | |
| | | 2.70 | | 100 | | |
| | | 3.00 | | 159 | | |
| J.T., 60 | 3.1 | 1.60 | 25 | | 120,000 | 20 |
| | 3.65 | 1.50 | 54 | | 262,000 | 25 |
| | 2.7 | 1.00 | 81 | | 392,000 | 19 |
| | | 1.25 | 112 | | 504,000 | 17 |
| | | 0.80 | 138 | | 712,000 | 21 |
| | | 0.75 | 164 | | 910,000 | 18 |
| | | 0.65 | 194 | | 1,156,000 | 22 |
| | | 0.45 | 221 | | 1,372,000 | 20 |
| | | 1.10 | | 49 | | |
| | | 2.80 | | 84 | | |
| | | 3.70 | | 109 | | |
| | | 3.85 | | 139 | | |
| M.G., 69 | 2.4 | 3.90 | 32 | | 90,000 | 15 |
| | 3.8 | 3.60 | 57 | | 152,000 | 11 |
| | 3.6 | 4.70 | 88 | | 197,000 | 13 |
| | 3.2 | 2.50 | 114 | | 251,000 | 9 |
| | | 4.25 | 144 | | 359,000 | 13 |
| | | 1.45 | 175 | | 474,000 | 12 |
| | | 2.90 | 209 | | 624,000 | 15 |
| | | 3.50 | 256 | | 862,000 | 20 |
| | | 2.25 | 291 | | 1,018,000 | 13 |
| | | 1.35 | 315 | | 1,114,000 | 8 |
| | | 1.60 | 342 | | 1,246,000 | 11 |
| | | 1.55 | 365 | | 1,354,000 | 9 |
| J.L., 72 | 4.1 | 2.85 | 32 | | 80,000 | 14 |
| | 3.6 | 1.40 | 56 | | 131,000 | 11 |
| | 2.3 | 3.25 | 92 | | 179,000 | 12 |
| | | 2.20 | 119 | | 263,000 | 12 |
| | | 1.40 | 145 | | 371,000 | 11 |
| | | 0.70 | 196 | | 587,000 | 21 |
| | | 3.00 | | 65 | | |
| | | 3.30 | | 93 | | |
| | | 2.50 | | 128 | | |
| W.B., 58 | 2.7 | 4.05 | 24 | | 66,000 | 11 |
| | 4.1 | 4.30 | 72 | | 186,000 | 20 |
| | | 2.40 | 117 | | 366,000 | 19 |
| | | 0.95 | 145 | | 510,000 | 12 |
| | | 0.70 | 180 | | 690,000 | 15 |

accurately. The semen was measured after liquefaction which usually occurred within 10 or 20 minutes after the specimen was obtained. During the time the patients were under observation the prostate gland was not massaged, and four or five days were allowed to elapse for patients who had had intercourse before specimens were taken.

In a previous report, we demonstrated that an androgenic substance, testosterone propionate, has very little, if any, effect upon the volume of seminal fluid in man (1). In animal experiments, it has been shown that estrogenic substances markedly decrease the volume of seminal fluid in dogs (2), and when injected in large doses they will produce atrophy of the

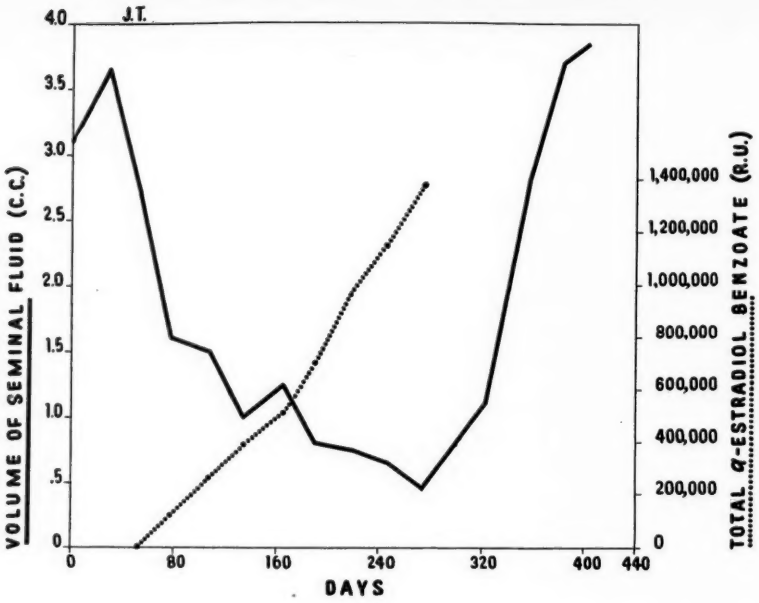
J.T.
VOLUME OF SEMINAL FLUID (C.C.)
TOTAL α-ESTRADIOL BENZOATE (R.U.)
DAYS
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0
1,400,000
1,200,000
1,000,000
800,000
600,000
400,000
200,000
0
0
80
160
240
320
400
440

Fig. 2

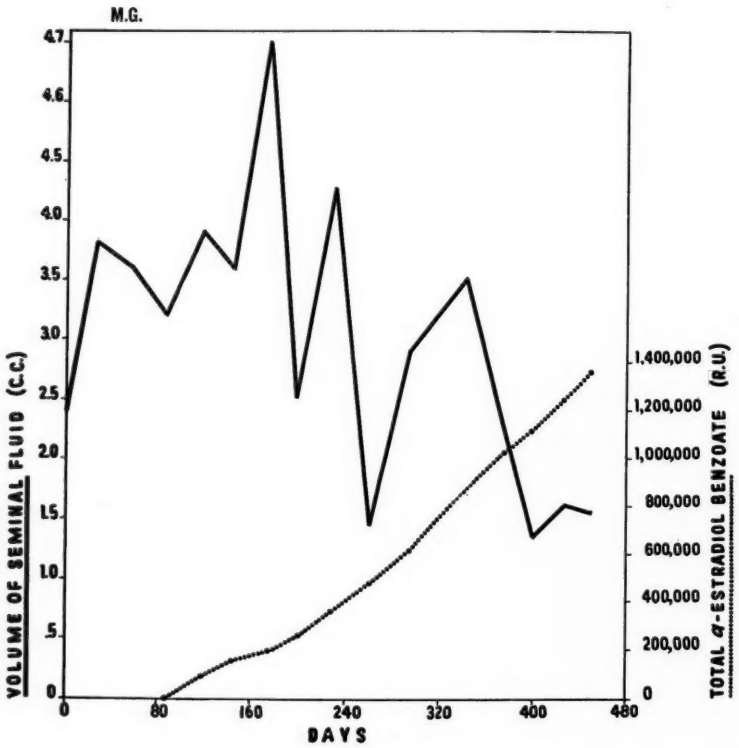
M.G.
VOLUME OF SEMINAL FLUID (C.C.)
TOTAL α-ESTRADIOL BENZOATE (R.U.)
DAYS
4.7
4.6
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0
1,400,000
1,200,000
1,000,000
800,000
600,000
400,000
200,000
0
0
80
160
240
320
400
480

Fig. 3

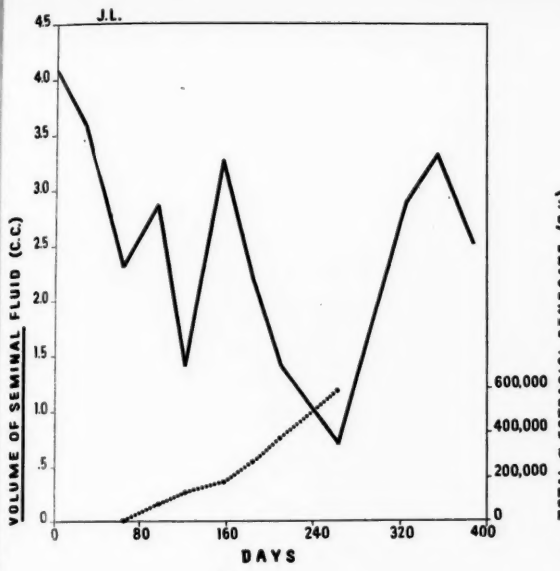


Fig. 4

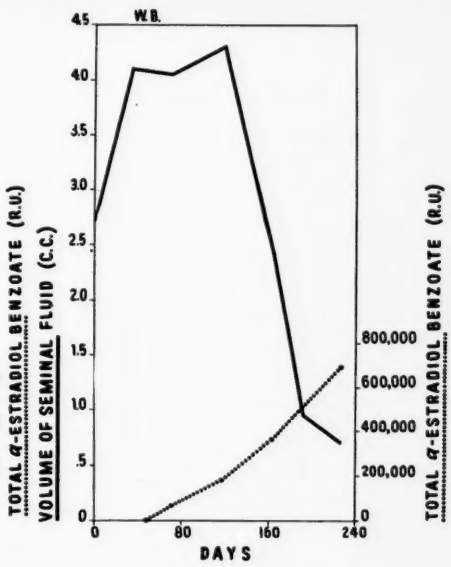


Fig. 5

testes, epididymides, seminal vesicles, and prostate in the rat (3).

## SUMMARY

The data presented here indicate that in man, as in dogs, estrogenic substances will cause a marked decrease in the volume of seminal fluid.

Since the volume of seminal fluid in the human is composed almost entirely of secretions from the prostate gland and seminal vesicles, it can be assumed that the secretory mechanism of the glands themselves is in some way affected by estrogens.

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# The Colorimetric Determination of Neutral Steroids (Hormones) in a 24-Hour Sample of Human Urine[1] (Pregnanediol; Total, Alpha and Beta Alcoholic, and Non-Alcoholic 17-Ketosteroids)

[Neutral Steroids]

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It is becoming increasingly apparent that measurements of the urinary steroids are of value in clinical diagnosis and in studies of human endocrine physiology. Relatively simple procedures for the determination of the total, alpha and beta alcoholic, and non-alcoholic neutral 17-ketosteroids in a single twenty-four-hour urine sample have been reported (1, 2). Astwood and Jones (3) have recently perfected a simple procedure for the gravimetric determination of pregnanediol. The present paper reports a method whereby both the 17-ketosteroids and the pregnanediol may be determined colorimetrically on a single twenty-four-hour urine specimen.

The method involves (*a*) the simultaneous hydrolysis and extraction of steroids from urine with carbon tetrachloride, (*b*) separation of the neutral steroids into ketonic and non-ketonic fractions with Girard's Reagent "T," (*c*) colorimetric determination of pregnanediol in the non-ketonic fraction after purification according to Astwood and Jones and (*d*) colorimetric determination of the 17-ketosteroids in the ketonic fraction as described elsewhere (4).

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[1] This work was aided in part by a grant from the Commonwealth Fund, New York.

## METHOD

*Hydrolysis, Extraction and Preparation of Neutral Fraction.* A twenty-four-hour urine is collected with 7 cc. of concentrated hydrochloric acid added as preservative. The urine is simultaneously hydrolyzed with 15 vol. % of concentrated hydrochloric acid and extracted with $CCl_4$ in a continuous extraction apparatus (5) as described elsewhere (4). The $CCl_4$ solution is evaporated to approximate dryness on a water bath. After cooling the residue is dissolved in 5 cc. of absolute ethanol and transferred quantitatively to a 250 cc. separatory funnel with 150 cc. ethyl acetate, C.P. The ethyl acetate solution is washed four times with 25 cc. lots of aqueous normal NaOH and three times with 25 cc. lots of water and then is evaporated to dryness on a water bath. Removal of last traces of water from the residue is facilitated by the addition and subsequent evaporation of small lots of anhydrous ethyl ether. The residue contains impurities, ketonic and non-ketonic neutral steroids.

*Separation of Ketonic and Non-Ketonic Steroids.* The following procedure is a modification of one described previously (4). Two hundred mg. of Girard's Reagent "T"[2] and 0.5 cc. of glacial acetic acid are added to the dry residue. The flask containing the

mixture is stoppered with tinfoil and heated on the boiling water bath for 10 minutes. After the mixture has been cooled, it is dissolved in 7 cc. of ethanol, and 40 cc. of ice water containing 0.3 gm. NaOH are added. This mixture is extracted 4 times with 40 cc. portions of ethyl acetate, C.P. The combined ethyl acetate extracts, after being washed 3 times with 20 cc. portions of water, are evaporated to dryness. The residue is dissolved in 100 cc. of toluene, C.P. This non-ketonic fraction contains the pregnanediol.

The water washings of the above ethyl acetate extract are acidified with 1 cc. of concentrated $H_2SO_4$ and this solution is added to the aqueous phase remaining after the ethyl acetate extraction of the non-ketonic fraction. The acidified mixture is layered with 20 cc. of ethyl ether and allowed to stand 1½ hours at room temperature. It is then extracted with four 40 cc. lots of ethyl ether. The ethereal extract, after being washed once with 20 cc. of 0.1 N aqueous NaOH and 3 times with 20 cc. portions of water, is evaporated to dryness. The residue is dissolved in a measured volume of absolute ethanol. This ketonic fraction contains the 17-ketosteroids.

*Colorimetric Assay of the Neutral 17-Ketosteroids.* The total, alpha and beta alcoholic, and non-alcoholic neutral 17-ketosteroid content of the ketonic fraction is determined by procedures described elsewhere (1, 2, 4).

*Purification of Pregnanediol:* The procedure employed is essentially that described by Astwood and Jones (3) and is summarized as follows. To the toluene solution of the non-ketonic substances, 8 cc. of a 2% solution of NaOH in absolute methanol are added. The mixture is boiled on a Wood's metal bath until the alcohol has boiled off and the toluene solution has been reduced to half its original volume. The hot

TABLE 1. EXTINCTION COEFFICIENTS OF COLORED COMPOUND FORMED BY $H_2SO_4$ AND 0.8 MG. OF PREGNANEDIOL

| | Approximate wavelength in mμ. | | |
|---|---|---|---|
| | 420 | 540 | 660 |
| Extinction Coefficient | .81 | .12 | .01 |

toluene solution is poured through a sintered glass filter and the abundant gelatinous precipitate is washed with three 10 cc. lots of hot toluene C.P. This precipitate is discarded. The filtrate is evaporated to dryness on the Wood's metal bath, the last traces of toluene being carefully removed by a stream of air to avoid overheating the residue. Ten cc. of absolute ethanol are added and the residue is dissolved by heating on the water bath. While heating is continued, 40 cc. of aqueous 0.1 N NaOH are added slowly. The flask is stoppered and placed in the refrigerator overnight. The precipitated pregnanediol is collected on a sintered glass filter and washed thoroughly with water. After a final washing with a few cc. of petroleum ether the precipitate is transferred to a small flask with hot absolute ethanol. The solution is evaporated to dryness and the residue is dissolved in a measured quantity of fresh absolute ethanol.

*Colorimetric Assay of Pregnanediol:* An aliquot of the alcohol solution of the precipitate is transferred to a colorimeter tube of an Evelyn or other suitable

TABLE 2. SAMPLE EXPERIMENT TAKEN FROM SERIES ESTABLISHING PROPORTIONALITY CONSTANT BETWEEN TOTAL CRYSTALLINE PREGNANEDIOL DETERMINED IN SAMPLE AND AMOUNT SHOWN BY GALVANOMETER READING

| Total pregnanediol in sample analyzed | Galvanometer reading | K |
|---|---|---|
| mg. | | |
| 0.05 | 77 | .227 |
| 0.10 | 60[2] | .218 |
| 0.15 | 46 | .224 |
| 0.20 | 35[2] | .225 |
| 0.25 | 28 | .222 |
| 0.30 | 21[2] | .228 |
| Average | | .224 |

photoelectric colorimeter. The alcohol solution is evaporated to dryness by passing a slow stream of air over the solution as it is warmed on a water bath. Ten cc. of concentrated $H_2SO_4$, C.P. are added. The resulting solution and a blank prepared with absolute alcohol containing no pregnanediol, are allowed to stand at room temperature for 20 minutes with occasional stirring. By means of a filter with maximum transmission at 420 mμ, range 380 to 480 mμ, the galvanometer with the colorimeter tube containing the blank in place is adjusted to the desired reading. The tube is then replaced by that containing the unknown sample, and the galvanometer reading of the unknown is obtained. When the galvanometer reading of the blank is set at 100 in the Evelyn photoelectric colorimeter, the mg. of pregnanediol in the sample analyzed are calculated from the equation $C = (2 - \log g)/K$ where g is the galvanometer reading of the unknown and K is the constant of proportionality determined from solutions containing known amounts of pregnanediol (.05 to 0.3 mg.). Differences in the concentration of different batches of $H_2SO_4$ alter the K value slightly. A simple method of compensating for these differences in acid concentration is to set up a standard instead of a blank tube, and adjust the galvanometer so that the standard gives the correct reading, instead of adjusting the blank to 100.

[2] Trimethylacethydrazide ammonium chloride, Eastman Kodak Co.

## RESULTS

*Pregnanediol calibration curve:* An approximate extinction-wavelength curve of the colored compound formed by the addition of concentrated $H_2SO_4$ to dry pregnanediol has been determined by the use of light filters in the photoelectric colorimeter. The results shown in table 1 indicate that the maximum extinction coefficient was obtained with a 420 mμ filter.

The data obtained from a single representative experiment in establishing our calibration curve and constant of proportionality (*K* in the equation above) are presented in table 2. They indicate that crystalline pregnanediol in amounts ranging from .05 to .3 mg. per sample analyzed may be determined with an error of approximately 3%.

*Recovery of Pregnanediol and 17-Ketosteroid Added to Urine.* Recovery experiments were carried out in which known amounts of free pregnanediol and dehydroisoandrosterone were added to aliquots of pooled adult urine, the pregnanediol and 17-ketosteroid content of which were known. The analytical data from three series of such recovery experiments are given in table 3. The theoretical values represent the sum of the control value and the mg. of crystalline hormone added to each aliquot. The data show that over 90% of the steroid hormones added are recovered by this procedure.

*Time Required for Extraction of Pregnanediol from Water or Urine by Simultaneous Hydrolysis and Extraction with Carbon Tetrachloride.* Table 4 presents two experiments in which crystalline sodium pregnanediol glucuronidate was added to water and urine, respectively. After adding HCl, the mixture was simultaneously extracted, heated and hydrolyzed for measured periods of time (4). The data show that over 90% of the maximal free pregnanediol recovered was extracted during the first 6 hours. Data have been presented elsewhere (4) which indicate that the urinary 17-ketosteroids are also essentially completely extracted during the first six hours of this simultaneous hydrolysis and extraction procedure.

*Recovery of Sodium Pregnanediol Glucuronidate as Free Pregnanediol and of 17-ketosteroids after Simultaneous Hydrolysis and Extraction with Carbon Tetrachloride.* Recovery experiments were carried out in which measured amounts of crystalline sodium pregnanediol glucuronidate and/or dehydroisoandrosterone were added to aliquots of pooled adult urine or water, the pregnanediol and 17-ketosteroid content of which was known. The analytical data from four series of such experiments are given in table 5. The theoretical values for the 17-ketosteroids represent the sum of the control value of each urine sample and the mg. of crystalline ketosteroid added; the theoretical values for the pregnanediol were obtained by adding to the control pregnanediol value the product obtained by multiplying the mg. sodium pregnanediol glucuronidate by the factor 0.597.[3]

TABLE 3. RECOVERY OF PREGNANEDIOL AND A 17-KETOSTEROID ADDED TO URINE BEFORE SIMULTANEOUS HYDROLYSIS AND EXTRACTION WITH $CCl_4$. RESULTS EXPRESSED IN MG. PER LITER

| Exper. No. | Hormone added[1] | Pregnanediol | | | 17-Ketosteroid | | |
|---|---|---|---|---|---|---|---|
| | | Determined (A) | Theoretical (B) | A/B | Determined (C) | Theoretical (D) | C/D |
| 1. a. | None | 0.3 | — | — | 6.8 | — | — |
| b. | P(52)+ DHA (6.6) | 49.0 | 52.3 | .94 | 12.6 | 13.4 | .94 |
| 2. a. | None | 0.3 | — | — | 10.2 | — | — |
| b. | P(24)+ DHA (10.5) | 22.5 | 24.3 | .93 | 19.2 | 20.7 | .93 |
| 3. a. | None | 1.0 | — | — | 5.1 | — | — |
| b. | P (12) | 12.0 | 13.0 | .92 | 5.4 | — | — |
| Average | | | | .93 | | | .94 |

[1] P, pregnanediol; DHA, dehydroisoandrosterone. The figures in parentheses indicate the mg. of steroid added.

TABLE 4. TIME REQUIRED FOR SIMULTANEOUS HYDROLYSIS OF SODIUM PREGNANEDIOL GLUCURONIDATE WITH HCl AND EXTRACTION OF LIBERATED PREGNANEDIOL WITH $CCl_4$

| Experiment No. | Solution extracted | Total time | Total pregnanediol recovered | % total pregnanediol recovered |
|---|---|---|---|---|
| | | *hr.* | *mg.* | |
| 4. | water+sod. preg. glucuron. | 3 | 6.0 | 52 |
| | | 6 | 10.8 | 93 |
| | | 9 | 11.6 | 100 |
| 5. | urine+sod. preg. glucuron. | 3 | 7.4 | 57 |
| | | 6 | 12.9 | 100 |
| | | 9 | 12.9 | 100 |

[3] Analysis of the sodium pregnanediol glucuronidate (m.p.

TABLE 5. RECOVERY OF SODIUM PREGNANEDIOL GLUCURONATE AS PREGNANEDIOL AND OF 17-KETOSTEROIDS AFTER SIMULTANEOUS HYDROLYSIS AND EXTRACTION WITH $CCl_4$. Results expressed in mg. per liter

| Experiment No. | Hormone added[1] | Pregnanediol | | | 17-ketosteroid | | |
|---|---|---|---|---|---|---|---|
| | | Determined (A) | Theoretical (B) | A/B | Determined (C) | Theoretical (D) | C/D |
| 6. | NaPg (28) to water | 9.2 | 16.7 | .55 | — | — | — |
| 7. a. | DHA (6.6) | 0.3 | — | — | 14.0 | 12.7 | 1.1 |
| b. | NaPg (14.9) | 6.2 | 9.2 | .67 | 6.1 | — | — |
| 8. a. | None | 0.6 | — | — | — | — | — |
| b. | NaPg (20) | 7.0 | 12.5 | .56 | — | — | — |
| c. | NaPg (20) | 7.2 | 12.5 | .58 | — | — | — |
| d. | NaPg (20) | 8.1 | 12.5 | .65 | — | — | — |
| 9. a. | None | 0.3 | — | — | 10.2 | — | — |
| b. | NaPg (6)+ DHA (5.2) | 2.4 | 3.9 | .62 | 14.6 | 15.4 | .95 |
| | Average | | | .61 | | | .98 |

[1] NaPg, sodium pregnanediol glucuronidate; DHA, dehydroisoandrosterone. The figures in parentheses indicate the mg. of steroid added.

The recovery of added 17-ketosteroid averaged 98%. The yield of free pregnanediol was reasonably consistent and averaged 61% of the theoretical value.

277–278°C.) used in these experiments showed the following:

| | C | H | Na |
|---|---|---|---|
| Calculated for $C_{27}H_{45}O_8Na$ | 62.5 | 8.3 | 4.4 |
| Calculated for $C_{27}H_{45}O_8Na\ H_2O$ | 60.5 | 8.2 | 4.3 |
| Found | 59.9 | 8.9 | 4.0 |

This analytical finding is interpreted to signify that the sample of sodium pregnanediol glucuronidate contained one molecule of water of crystallization. Theoretically, therefore, 0.597 mg. of free pregnanediol should be obtained by hydrolysis of one mg. of the complex.

Astwood and Jones (3) obtained a slightly higher yield (average 68% of theoretical) of free pregnanediol from the pregnanediol complex by their procedure.

*Recovery of Sodium Pregnanediol Glucuronidate as Free Pregnanediol and of 17-ketosteroids after Simultaneous Hydrolysis and Extraction with Toluene.* The recovery experments shown in table 6 were the same as those presented in table 5 except that the urine was simultaneously hydrolyzed and extracted for 15 minutes with 10 vol. % HCl under a layer of toluene

TABLE 6. RECOVERY OF SODIUM PREGNANEDIOL GLUCURONIDATE AS PREGNANEDIOL AND OF 17-KETOSTEROIDS AFTER SIMULTANEOUS HYDROLYSIS AND EXTRACTION WITH TOLUENE. Results expressed as mg. per liter

| Experiment No. | Hormone added[1] | Pregnandiol | | | 17-Ketosteroid | | |
|---|---|---|---|---|---|---|---|
| | | Determined (A) | Theoretical (B) | A/B | Determined (C) | Theoretical (D) | C/D |
| 10. a. | NaPg (28) | 12.0 | 16.7 | .72 | — | — | — |
| b. | NaPg (28) | 11.0 | 16.7 | .66 | — | — | — |
| c. | NaPg (56) added to water | 24.0 | 33.5 | .72 | — | — | — |
| 11. a. | None | 0.2 | — | — | 1.7 | — | — |
| b. | NaPg (28) +DHA (4.6) | 12.5 | 16.9 | .74 | 5.4 | 6.3 | .86 |
| 12. a. | None | 0.2 | — | — | 2.4 | — | — |
| b. | NaPg (45) | 18.2 | 27.1 | .67 | 2.8 | — | — |
| c. | P (8.5)+ DHA (4.7) | 7.8 | 8.7 | (.90)[2] | 5.9 | 7.3 | .81 |
| 13. a. | None | 0.2 | — | — | 2.0 | — | — |
| b. | NaPg (6)+ DHA (11.5) | 2.7 | 3.8 | .71 | 10.9 | 13.5 | .81 |
| | Average | | | .70 | | | .83 |

[1] NaPg, sodium pregnanediol glucuronidate; P, pregnanediol; DHA, dehydroisoandrosterone. The figures in parentheses indicate the mg. of steroid added.

[2] This value represents the recovery of free pregnanediol added, and is therefore not included in the average.

as described by Astwood and Jones. (3) The extract obtained was treated as described above under method. It will be seen that the average yield (70%) of free pregnanediol from the sodium pregnanediol glucuronidate was slightly greater than the average yield (61%) obtained when the $CCl_4$ hydrolysis and extraction procedure was used (table 5). On the other hand, the recovery of 17-ketosteroids was more satisfactory when $CCl_4$ was used (average, 98%, table 5) than when the toluene procedure was employed (average 83%, table 6).

*Determination of Pregnanediol; total, alpha and beta alcoholic, and non-alcoholic 17-ketosteroids on a liter sample of urine.* An experiment designed to illustrate the approximate accuracy of the combined colorimetric methods for neutral urinary steroids is presented in table 7. For this experiment a pooled collection of male urine was obtained. To 1 liter aliquot, nothing was added. To each of 3 other liter aliquots a measured amount of pregnanediol and a beta alcoholic (dehydroisoandrosterone), alpha alcoholic (androsterone) or a non-alcoholic (3-chlorodehydroisoandrosterone) 17-ketosteroid were added. The theoretical values represent the sum of the control value and the mg. of the respective hormone added. The data show a satisfactory agreement between the determined and theoretical values.

TABLE 7. ILLUSTRATIVE EXPERIMENT OF FRACTIONATION AND COLORIMETRIC ASSAY OF PREGNANEDIOL, TOTAL, ALPHA AND BETA ALCOHOLIC, AND NON-ALCOHOLIC 17-KETOSTEROIDS ADDED TO URINE. Results expressed in mg. per liter of urine

| Hormone added[1] | Pregnanediol | | 17-Ketosteroids | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | total | | alcoholic | | | | non-alcoholic | |
| | | | | | alpha | | beta | | | |
| | determined | theoretical | determined | theoretical | determined | theoretical | determined | theoretical | determined | theoretical |
| None | 0.0 | — | 5.6 | — | 4.3 | — | 0.9 | — | 0.4 | — |
| P (2.8)+ DHA (5.9) | 2.0 | 2.8 | 10.1 | 11.5 | 4.3 | 4.3 | **5.3** | **6.8** | 0.5 | 0.4 |
| P (5.6)+ A(4.7) | 5.6 | 5.6 | 10.4 | 10.3 | **9.5** | **9.0** | 0.4 | 0.9 | 0.5 | 0.4 |
| P (11.2)+ CLDHA (4.4) | 10.9 | 11.2 | 11.1 | 10.0 | 5.7 | 4.3 | 0.9[2] | 0.9 | **4.5** | 4.8 |

[1] P, pregnanediol; DHA, dehydroisoandrosterone; A, androsterone; CLDHA, chlorodehydroisoandrosterone. The figures in parentheses indicate the mg. of steroid added.

[2] Although chlorodehydroisoandrosterone is a non-alcoholic compound, it appears in the beta fraction after precipitation with digitonin (4). Therefore, in this experiment the digitonin precipitation was carried out both on an aliquot of the ketonic fraction before the alcoholic and non-alcoholic ketosteroids had been separated and on an aliquot of the non-alcoholic fraction. The beta alcoholic value shown in the table represents the total apparent "beta ketosteroids" minus the non-alcoholic "beta ketosteroids."

## DISCUSSION

The purpose of these studies has been to devise reasonably accurate and simple procedures which could be applied to clinical studies of urinary steroid hormone excretion. For this purpose it has seemed desirable to be able to determine as many different steroid constituents as possible on a single twenty-four-hour sample of urine. The procedures described previously for the colorimetric assay of 17-ketosteroid constituents did not provide for the assay of pregnanediol. On the other hand, preliminary studies in this laboratory revealed that the method of Astwood and Jones (3) for the gravimetric assay of pregnanediol could not be adapted to include the assay of urinary 17-ketosteroids without major modifications because their procedure for the purification of pregnanediol causes a significant loss of 17-ketosteroids. This difficulty has been overcome by purifying the pregnanediol after separating it from the ketosteroids by means of Girard's Reagent "T."

The fact that pregnanediol and certain other steroid compounds react with sulfuric acid to give a color has been described previously (6). Because the color reaction is not specific (6, 7) isolation of pregnanediol in relatively pure state is essential. The melting point of several samples of pregnanediol obtained from urine by the procedure described here has been determined and found to be about 230°C. (pure pregnanediol 237–8°C.). Furthermore, the colorimetric determination of pregnanediol has been checked repeatedly by gravimetric measurements. In no instance did the value obtained by colorimetric assay exceed the value obtained by gravimetric measurement; in the majority of instances the two assay values agreed within 10%.

The failure to recover the theoretical amount of free pregnanediol from sodium pregnanediol glucu-

ronidate by hydrolysis of the latter compound remains unexplained. The same difficulty has been encountered by others (3). From the point of view of clinical assay, the loss is not significant because it is consistent.


## SUMMARY

Procedures are described for the determination of the pregnanediol and the total, alpha and beta alcoholic, and non-alcoholic 17-ketosteroids on a single twenty-four-hour sample of human urine. The methods employed are relatively simple and are suitable for routine clinical use.


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# Prophylactic Implantation of Estrogens in Ovariectomized Women[1]

## [Estrogens in Surgical Menopause]

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A VARIETY of studies have established the fact that removal of both ovaries in animals, as well as in women, is followed by a disturbance of the normal sex endocrine balance (1–8). In women, this imbalance is manifested (*a*) by the excretion of excessive amounts of gonadotropic hormone (9–14) which can be detected as early as 3 days after ovariectomy (15); (*b*) by progressive involutional changes in the uterus and vagina and (*c*), clinically, by the onset of the distressing menopause symptoms. It has, furthermore, been shown that these symptoms can be relieved, the excessive secretion of gonadotropic hormone suppressed (6, 16–20), and the involutional changes in the genital tract restored to the physiological state by the administration of adequate amounts of estrogens (17, 19–26). It therefore seemed logical, when removal of both ovaries is necessary, to attempt to prevent the endocrine imbalance with its concomitant distressing symptoms, by administering estrogens at the time of ovariectomy.

Previous studies have demonstrated the advantages of the implantation of pure crystalline estrogenic hormone over other methods of estrogen therapy in the treatment of the menopause syndrome (27–31). The superiority of implantation over other methods of estrogen administration was shown by the prolonged period of symptomatic relief (27, 29, 30), as well as by the duration of pituitary inhibition (29) and of morphologic evidence of estrogenic effects on the endometrium and vaginal mucosa (27, 32). Thus it was demonstrated that, as a result of the implantation of estradiol crystals in ovariectomized women, the excessive gonadotropic hormone excretion can be suppressed for as long as 149 days and morphologic evidence of estrogenic activity can be found in the vaginal mucosa as long as 7 months after the implantation (32). One year ago, in a communication presented before the Association, describing the physiologic effects of estrogen implantation, we included a preliminary report on the therapeutic results of prophylactic estrogen implantation in a series of 10 ovariectomized women. At the time of the report, which was 12 months after the first prophylactic implantation had been performed, none of the patients had developed any symptoms. At present, we wish to report our further observations in a series of 36 ovariectomized women who were implanted prophylactically with estrogens and who have been observed for periods extending up to 23 months.

### PROCEDURE

The study was conducted on 36 women upon whom hysterectomy and bilateral ovariectomy were performed for either uterine fibroids or chronic adnexitis or both. The patients' ages varied from 40 to 52 years.

Implantations were performed with compressed pellets and loose crystals of $\alpha$-estradiol, $\alpha$-estradiol benzoate and $\alpha$-estradiol dipropionate. The amount of hormone implanted varied from 15 to 30.8 mg. The implantations were made in the subcutaneous fatty tissues of the outer and upper aspect of the thigh. The technic of the implantation has been previously described (27). Details of the individual cases are given in table 1.

### RESULTS

The post-implantation period of observation varied from 3 to 23 months. The effectiveness of the therapeutic prophylactic action of the implantation was

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TABLE 1. DURATION OF PROPHYLACTIC EFFECT OF ESTROGEN IMPLANTS IN WOMEN FOLLOWING BILATERAL OÖPHORECTOMY

| No. | Age | Hormone | Wt. | Months symptom-free | Remarks |
|---|---|---|---|---|---|
| | | | *mg.* | | |
| 1 | 40 | Estradiol benzoate crystals | 25.0 | 19+ | Never experienced flushes |
| 2 | 43 | | 23.0 | 12 | One weak flush every few days; required no treatment |
| 3 | 47 | | 29.0 | 8+ | Never experienced flushes |
| 4 | 39 | | 30.0 | 11 | Has 1–2 weak flushes daily; required no treatment |
| 5 | 38 | | 30.0 | 5 | Has 1–2 flushes daily; required no treatment |
| 6 | 43 | | 27.0 | 6+ | Never experienced flushes |
| 7 | 41 | | 30.0 | 6+ | Never experienced flushes |
| 8 | 42 | | 30.0 | 5+ | Never experienced flushes |
| 9 | 45 | | 26.6 | 6+ | Never experienced flushes |
| 10 | 44 | | 30.0 | 6 | Frequent flushes; required treatment |
| 11 | 39 | | 30.0 | 6 | Frequent flushes; required treatment |
| 12 | 50 | | 30.8 | 8 | 8–10 flushes daily; required treatment. Re-implanted with estradiol dipropionate pellets with relief of symptoms |
| 13 | 45 | | 28.4 | 4 | Frequent flushes; required treatment |
| 14 | 40 | | 25.4 | 10 | Developed flushes 4 mo. after implantation. The symptoms lasted for 2 mo. and then subsided without further therapy |
| 15 | 45 | | 25.0 | 6 wk. | Convalescence complicated by myocardial infarction; at 6 wk. developed 1 or 2 weak flushes per day for several weeks; at 4 mo. has an occasional faint flush which required no treatment |
| 16 | 47 | | 26.0 | 4+ | Never experienced flushes |
| 17 | 50 | | 22.0 | 7+ | Never experienced flushes |
| 18 | 46 | | 27.0 | 17 | 1–2 faint flushes per day; required no treatment |
| 18 | 43 | | 23.7 | 23 | 1–2 faint flushes per day; required no treatment |
| 19 | 40 | | 25.9 | 11 | 2–3 faint flushes per day; required no treatment |
| 20 | 41 | Estradiol benzoate pellets | 25.0 | 17+ | Never experienced flushes |
| 21 | 46 | | 25.0 | 5+ | Never experienced flushes |
| 22 | 41 | | 15.0 | 4+ | Never experienced flushes |
| 23 | 36 | | 15.0 | 10 | 1–2 flushes per day; required no treatment |
| 24 | 50 | Estradiol dipropionate crystals | 23.0 | 8+ | Never experienced flushes |
| 25 | 45 | | 23.0 | 8 | Frequent flushes, re-implanted with estradiol dipropionate pellets, followed by disappearance of flushes |
| 26 | 47 | | 23.0 | 10 | 1–2 flushes daily; required no treatment |
| 27 | 40 | | 23.0 | 4 | Severe symptoms; required treatment |
| 28 | 40 | Estradiol crystals | 29.0 | 9 | 1–2 weak flushes daily; required no treatment |
| 29 | 49 | | 30.0 | 6+ | Never experienced flushes |
| 30 | 42 | | 24.6 | 9½+ | Never experienced flushes |
| 31 | 45 | | 25.3 | 17 | 2–3 faint flushes daily; required no treatment |
| 32 | 42 | Estradiol pellets | 50.0 | 3+ | Never experienced flushes |
| 33 | 44 | | 50.0 | 4+ | Never experienced flushes |
| 34 | 44 | | 50.0 | 3+ | Never experienced flushes |
| 35 | 46 | | 50.0 | 4+ | Never experienced flushes |
| 36 | 43 | | 52.0 | 6 | 1–2 weak flushes daily; required no treatment |

measured by the time elapsed between the ovariectomy and the onset of flushes. Of the 36 implanted cases, only one (*case 15*)[2] developed flushes during the first 3 months after implantation. Of the 28 patients in the series who have been observed for 5 months or longer, 12 were completely free of symptoms, 12 had occasional faint flushes which required no treatment, and 4 had frequent flushes requiring additional estrogen therapy. Of the entire series of 36 cases, 18 have remained completely symptom-free during the period of observation (3 to 23 months). In attempting to evaluate the therapeutic effectiveness of the prophylactic estrogen implantation, one must recognize the fact that in a given untreated case it is impossible to predict the date of onset of symptoms and their severity. A number of uncontrollable elements, such as the stability of the autonomic nervous system of the individual, the emotional make-up of the patient, as well as environmental factors, undoubtedly influence both the patient's somatic response to the estrogen deprivation as well as her psychic reaction to the castration. With full realization that it would be well nigh impossible to control all of these complex

[2] The unusually early onset of symptoms in this patient may have been related to the fact that her convalescence was complicated by a myocardial infarction.

factors, we have, nevertheless, attempted to determine how soon after removal of both ovaries characteristic symptoms appear in the majority of patients. The incidence and date of onset of flushes in an untreated group of 88 patients, is shown in table 2. It will be noted that 26% developed symptoms within one week after bilateral oöphorectomy; 42% within 2 weeks; and 89% within 12 weeks. In contrast to these, none of the implanted cases, with but one exception,[2] developed symptoms during the first 3 months after the estrogen implantation. Furthermore, when symptoms did appear in the implanted patients, they were usually mild and showed very little tendency to progression.

TABLE 2. INCIDENCE OF FLUSHES AFTER BILATERAL OVARIECTOMY IN 36 PATIENTS IMPLANTED WITH ESTROGENS AND 88 CONTROLS

| Time after ovariectomy, wk. | No. of untreated patients having flushes | % | No. of implanted patients having flushes | % |
|---|---|---|---|---|
| 1 | 23 | 26 | 0 | 0 |
| 2 | 37 | 42 | 0 | 0 |
| 3 | 49 | 56 | 0 | 0 |
| 4 | 55 | 62 | 0 | 0 |
| 6 | 71 | 81 | 1 | 3 |
| 12 | 78 | 89 | 1 | 3 |

In addition to its beneficial somatic effects, the estrogen implantation has distinct psycho-therapeutic value by virtue of its suppression of the flushes which constitute, to the patient, a reminder of the castration and its implications. Sparing the patient this psychic trauma is particularly important when the patient is distressed by the usual postoperative discomforts.

## SUMMARY AND CONCLUSIONS

In an attempt to prevent the onset of menopausal symptoms which result from bilateral ovariectomy, a series of 36 patients was implanted with crystals and pellets of α-estradiol, α-estradiol benzoate and α-estradiol dipropionate.

At the end of 4 weeks, none of the implanted patients had symptoms, whereas 62% of the control series had typical symptoms. At the end of 3 months, only 3% of the implanted series had symptoms, in contrast to 89% of the control group.

Of the 36 implanted patients 18 experienced no flushes during the period of observation which varied from 3 to 23 months.

From these observations, it appears that the usual menopause symptoms which result from removal of both ovaries in women, can be held in abeyance by the implantation of crystalline estrogenic hormone at the time of ovariectomy. The duration of the prophylactic action of the estrogen implantation has varied from 6 weeks to upwards of 23 months.

On the basis of this study, prophylactic implantation of estrogens is recommended because of its beneficial somatic and psycho-therapeutic effects.

By repeating the estrogen implantations, it may be possible to prevent the occurrence of the menopausal symptoms permanently.

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# Effective Therapy of the Menopause Using Estrogen in Lower Dosage

[Estrogens in Menopause]

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ALTHOUGH the literature is replete with studies establishing the value of estrogenic substance replacement in the treatment of menopausal syndromes and therefore, it is not the purpose of this paper merely to confirm previously determined facts relative to the subject, the problem of dosage of estrogenic hormone in given clinical syndromes has not received as much attention as it merits. It has long been the author's conviction that estrogen dosages, as empirically administered by many physicians, are so high that they are entirely disproportionate to the symptomatology which they are intended to relieve. It is difficult to know why this should be. According to Wolf,[1] "The dosage [of estrogen in the menopause] should be the smallest possible which will give relief . . . gradually increasing the dose until clear-cut results are evident. At times surprisingly low amounts are sufficient." Adair[2] claims, "Small amounts of estrogenic substances, insufficient to produce menstruation, will suffice to affect the vasomotor and psychic manifestations of the menopause." The present study was undertaken with these and similar generalizations in mind. Borne in mind also were the thoughts that a considerable psychic benefit might be gained through having the patients realize that her symptoms were not so alarming as to require high dosage and that the smaller cost of lower dosage could make the treatment more readily available from the economic point of view.

To test the clinical soundness of the foregoing premise it was decided to study the effects of treatment in 40 menopausal women grouped according to extent, duration and severity of their symptomatology and given estradiol benzoate[3] in doses the highest of which was much lower than that frequently prescribed in similar clinical circumstances. Thirty-five of these menopausal cases were spontaneous; five were induced. Their presenting symptoms are listed and classified below.

1. Menstrual irregularities
   *a*) Abrupt cessation
   *b*) Oligomenorrhea
   *c*) Metrorrhagia
   *d*) Menorrhagia
2. Psychogenic symptoms
   *a*) Emotional instability and irritability
   *b*) Depression
   *c*) Involutional psychosis
3. Neuro-circulatory vasomotor disturbances
   *a*) Hot flashes
   *b*) Excessive perspiration
   *c*) Sensitivity of heat or cold
   *d*) Acra-parasthesias
   *e*) Headache
4. Parasympathetic-sympathetic nervous system symptoms
   *a*) Spastic colon (mucous colitis)
   *b*) Pylorospasm
   *c*) Palpitation
   *d*) Dryness of mouth
5. Metabolic
   *a*) Obesity
   *b*) Fatigue
   *c*) Metabolic arthralgias, myalgias, etc.

By thus classifying the patients according to their presenting symptoms the severity of the menopausal syndrome of each can be noted. For example, the patient who suffers from at least one condition in each of the five symptom-groups listed, would be classified as 1 through 5, and her menopausal syndrome, accordingly, considered very severe. Only 6 of the entire group of patients were considered as representative of this type case. As may be seen in the table, other patients are classified as 1 through 3, 1 and 3, 3 through 5, and so on. The assignment of symptom-group numbers means that the patient presented mainly symptoms of the corresponding group.

The duration of symptoms was on the average from 2 to 5 years both in the spontaneous and induced cases. In the occasional case the clinical picture was confusing, particularly in those in which typical menstrual symptoms appeared as much as a year in

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[1] "Endocrinology in Modern Practice," Saunders.

[2] "Obstetrics and Gynecology," Lea & Febiger.

[3] As Dimenformon Benzoate, Roche-Organon, Nutley, N.J.

advance of any menstrual changes. Several cases presented typical menopausal pictures years after cessation of menses coincident to hysterectomy.

Therapeutic response was considered successful as soon as a patient's chief complaints or most aggravated symptoms were relieved, complete eradication of the entire syndrome not being considered the sole test of therapeutic successes after the lower dosage herein discussed had produced almost immediate complete symptomatic relief.

Each of the patients in this series was given estrogenic substance in varying dosage over a period of 3 months or more. The material used was estradiol benzoate in 600, 1,000 and 2,000 R.U. doses, respec-

ESTRADIOL BENZOATE, NUMBER OF INJECTIONS AND DOSAGE IN WOMEN AT MENOPAUSE

| Number | Case Type | Severity of Symptoms | 14 Days R.U. | 14 Days R.U. | 14 Days R.U. | 14 Days R.U. | 14 Days R.U. | 14 Days R.U. | Results Good After: |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Menopause, spont. | 1 through 5 | 4— 600 | 4—1000 | 2—2000 | 3— 600 | 2— 600 | 2— 600 | 3rd period |
| 2 | | 1 through 5 | 2— 600 | 4— 600 | 4— 600 | 2—2000 | 2—2000 | 2—1000 | 5th period |
| 3 | | 1 through 5 | 2—2000 | 2—2000 | 2—1000 | 2—1000 | 2— 600 | 2— 600 | 1st period |
| 4 | | 3 through 5 | 4—1000 | 2—1000 | 2—1000 | 2— 600 | 2— 600 | 2— 600 | 2nd period |
| 5 | | 3 | 2—1000 | 2—1000 | 2— 600 | 2— 600 | 2— 600 | 2— 600 | 2nd period |
| 6 | | 5 | 4—1000 | 4—1000 | 4—1000 | 4—1000 | 2—1000 | 2—1000 | 3rd period |
| 7 | | 3 through 5 | 2— 600 | 2— 600 | 4— 600 | 4— 600 | 4—1000 | 2—2000 | 5th period |
| 8 | | 1 through 5 | 4—2000 | 2—2000 | 4—1000 | 2—1000 | 2—1000 | 2— 600 | 3rd period |
| 9 | | 4 and 5 | 2— 600 | 4— 600 | 4—1000 | 4—1000 | 4—2000 | 4—2000 | 5th period |
| 10 | | 1 through 5 | 2— 600 | 2—1000 | 2—2000 | 2—2000 | 2—1000 | 2— 600 | 3rd period |
| 11 | | 1 | 2— 600 | 2— 600 | 2— 600 | 2— 600 | 2— 600 | 2— 600 | 1st period |
| 12 | | 3, 4, and 5 | 1— 600 | 2— 600 | 3— 600 | 4— 600 | 4— 600 | 4— 600 | 4th period |
| 13 | | 1 through 5 | 2— 600 | 2— 600 | 2— 600 | 2—1000 | 2—2000 | 2—1000 | 5th period |
| 14 | | 1 through 5 | 2—2000 | 2—2000 | 2—1000 | 2—1000 | 2—1000 | 2— 600 | 1st period |
| 15 | | 1 through 3 | 2— 600 | 2— 600 | 2— 600 | 2—2000 | 2—2000 | 2—1000 | 5th period |
| 16 | | 1 through 3 | 4— 600 | 4— 600 | 4—1000 | 4—1000 | 2—1000 | 2— 600 | 4th period |
| 17 | | 1 through 3 | 4—1000 | 4—1000 | 4— 600 | 2—1000 | 2—1000 | 2—1000 | 1st period |
| 18 | | 1 through 3 | 2—1000 | 2—1000 | 2—1000 | 3— 600 | 3— 600 | 2— 600 | 2nd period |
| 19 | | 1 through 3 | 2—1000 | 2—1000 | 2—1000 | 3— 600 | 3— 600 | 1— 600 | 2nd period |
| 20 | | 1 through 3 | 2—1000 | 2—1000 | 2—1000 | 3— 600 | 3— 600 | 1— 600 | 2nd period |
| 21 | | 1 through 3 | 1—2000 | 1—2000 | 2—1000 | 2—1000 | 1—1000 | 1—1000 | 1st period |
| 22 | | 1 through 3 | 1—2000 | 2—2000 | 4—2000 | 2—2000 | 2—1000 | 2—1000 | 4th period |
| 23 | | 1 through 4 | 1—1000 | 2—1000 | 2—2000 | 2—1000 | 2—1000 | 1—1000 | 3rd period |
| 24 | | 1 through 4 | 2— 600 | 3— 600 | 2—1000 | 2—2000 | 2—1000 | 2—1000 | 4th period |
| 25 | | 1 through 4 | 2— 600 | 2—1000 | 2—2000 | 2—2000 | 2—2000 | 3— 600 | 3rd period |
| 26 | | 1 and 3 | 2—1000 | 2—1000 | 2— 600 | 2— 600 | 2— 600 | 1— 600 | 2nd period |
| 27 | | 1 and 3 | 4— 600 | 2— 600 | 2— 600 | 2— 600 | 2— 600 | 1— 600 | 1st week |
| 28 | | 1 and 3 | 4— 600 | 4— 600 | 2— 600 | 2— 600 | 1— 600 | 1— 600 | 1st week |
| 29 | | 1 and 3 | 2—1000 | 2—1000 | 2— 600 | 2— 600 | 2— 600 | 2— 600 | 2nd week |
| 30 | | 1 and 3 | 2—1000 | 2—1000 | 2— 600 | 2— 600 | 2— 600 | 2— 600 | 2nd week |
| 31 | | 1 and 3 | 2—1000 | 2—1000 | 2— 600 | 2— 600 | 1— 600 | 1— 600 | 2nd week |
| 32 | | 1 and 3 | 2—1000 | 2— 600 | 2— 600 | 1—1000 | 1— 600 | 1— 600 | 2nd week |
| 33 | | 1 and 3 | 2—1000 | 1—1000 | 2— 600 | 1— 600 | 1— 600 | 1— 600 | 2nd week |
| 34 | | 1 and 3 | 1—2000 | 1—1000 | 1— 600 | 1— 600 | 1— 600 | 1— 600 | 2nd week |
| 35 | | 1 and 3 | 1— 200 | 1—1000 | 1— 600 | 1— 600 | 1— 600 | 1— 600 | 2nd week |
| 36 | Menopause, induced | | 2— 600 | 2—1000 | 2—2000 | 4—2000 | 4—2000 | 2—2000 | 4th period |
| 37 | | | 2— 600 | 2—1000 | 2—2000 | 4—2000 | 4—2000 | 2—2000 | 4th period |
| 38 | | | 4—2000 | 4—2000 | 3—2000 | 3—2000 | 2—2000 | 2—2000 | 1st period |
| 39 | | | 2—2000 | 2—2000 | 4—2000 | 4—2000 | 4—2000 | 2—2000 | 3rd period |
| 40 | | | 2—2000 | 4—2000 | 4—2000 | 4—2000 | 2—2000 | 2—2000 | 2nd period |

the effectiveness of treatment. For example, a patient who ran the whole gamut of symptom-groups as here presented, but whose chief complaints were a feeling of chronic 'blueness' where heretofore her disposition had been happy, hot flashes and easy fatigability would be considered as having responded successfully after only these symptoms had been controlled. Similarly, those patients classified under symptom-group 3 only, and whose only complaints were obviously on a vasomotor basis, were classed as

tively, according to degree of severity of symptoms. All injections were given intramuscularly into the buttock. The results of varying doses and response may be noted in the table.

The 40 cases in the table are classified according to whether spontaneous or induced and as to symptom type. The dosage time is divided into six 2-week periods in which the respective doses given are indicated. In the result column the time required for a clinically satisfactory response is noted.

## RESULTS

In the majority of the spontaneous menopausal cases of moderate to great severity as indicated by numbers 1 through 3 or 1 through 5, the smallest unitage doses such as 600 and 1,000 were ineffective in the beginning of treatment but were effective after 4 or 5 periods of treatment with larger doses. For example, a patient may require two 2,000 R.U. injections weekly for 6 weeks, and subsequently remain very comfortable on one or two 600 R.U. injections weekly.

The results were different in the spontaneous menopausal groups of less severity, that is, presenting mainly group 3 symptoms. In this group only one or two 1,000 R.U. injections were required weekly for 4 weeks, after which one or two 600 R.U. doses were needed weekly. In some, only 600 R.U. doses were required for a 2-week period. *Case 26* was a typical example of this.

In the induced menopausal cases, the 600 and even the 1,000 R.U. doses failed to give satisfactory results. At least two 2,000 R.U. injections were required in each period for an effective response.

## SUMMARY AND CONCLUSIONS

A group of 40 cases, requiring estrogenic substance was studied as to dosage required. The group comprised 35 cases of spontaneous menopause of varying severity and 5 cases of induced menopause.

In the severe spontaneous menopausal cases, the 2,000 R.U. doses were mainly effective; the 1,000 and 600 R.U. doses yielding good results subsequently.

The milder spontaneous menopausal cases required only 600 to 1,000 R.U. injections for good results.

The induced menopausal cases responded only to the 2,000 R.U. doses given more frequently than in any of the other groups.

An attempt has been made to show that many cases requiring estrogen replacement therapy can be successfully treated with smaller doses than are often employed, and that this fact can result in considerable economic and psychologic benefit to the patient. In addition to being therapeutically sound, it can well mean that a patient can afford treatment of which she might otherwise be deprived.

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# Pitressin Tannate Therapy in Diabetes Insipidus

## [Diabetes Insipidus and Pitressin]

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IN RECENT YEARS VARIOUS TECHNICS have been employed to increase the efficacy of endocrine therapy by decreasing the rate of absorption of parenterally administered hormones (1–7). It is apparent that the clinical value of such efforts depends not only upon the effectiveness with which hormone absorption is delayed, but also upon the success with which the absorption of a relatively constant quantity of hormone meets physiological requirements. Thus it might be anticipated that delaying the absorption of hormones such as the estrogens and androgens would be more efficacious clinically than delaying the absorption of insulin, since in the case of the latter, there is a great increase in hormone requirement several times daily.

It would appear likely that in the case of pitressin a decrease in the rate of absorption might prove to be very efficacious clinically since it is well known that the most satisfactory regulation of the polydypsia and polyuria in patients with diabetes insipidus is obtained by administering repeated small doses of hormone.

Our interest in the use of pitressin tannate in oil was first aroused by the very great difficulty which had arisen in the control of polydypsia and polyuria in *patient H.H.* (see protocol). This patient had been forced to discontinue nasal insufflations of posterior pituitary extract because of local irritation and gastric distress. Unfortunately, relatively small doses of posterior pituitary extract, subcutaneously, were followed by severe abdominal cramps, frequently resulting in diarrhea and anorexia. Only by administering 0.1 to 0.2 cc. of posterior pituitary extract subcutaneously 4 to 6 times daily could her symptoms be moderated. On this regimen the 24-hour urine volume approximated 8 to 10 liters (in the absence of therapy, the urine volume frequently exceeded 20 liters per day).

Since Greene (8, 9) and Stephens (10) had reported success in the use of pitressin tannate in oil in the control of polydypsia and polyuria in experimental animals and in patients with diabetes insipidus, we decided to test the value of this preparation in our patient. The improvement which occurred in this severe case of diabetes insipidus was striking and extremely satisfactory. A description of the effect of pitressin tannate[1] therapy on the mineral and water balance of three patients with diabetes insipidus follows.

### METHODS

The patients were studied on the metabolism ward of the Johns Hopkins Hospital and were permitted water ad libitum. The fluid intake and urine volume were measured. Changes in mineral balance in relation to pitressin therapy were studied in *patients D.L.* and *D.B.* These patients were provided with a constant diet, the same items of food being ingested each day throughout the period of investigation. A quantity of food sufficient for a 5-day period was purchased at one time and an aliquot of one day's entire diet was analyzed for its mineral content. Since the food was prepared without added seasoning, each patient was permitted an accurately weighed quantity of sodium chloride (*patient D.L.*, 2 gm. and *patient D.B.*, 1 gm. daily) which was added to the food immediately before being ingested.

Specimens of blood for chemical analyses were withdrawn under oil and without stasis from the antecubital vein, the patients having fasted for 15 hours previously. The methods used in the chemical determinations of blood and urine specimens have been described (11).

Following a control period the patients were treated with intramuscular injections of pitressin in oil. Later, the treatment was discontinued for a variable period. During each of these periods the patients'

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[1] We are indebted to Doctor E. A. Sharpe of Parke, Davis and Company, Detroit, Michigan, for the pitressin tannate in oil which was provided for these studies.

clinical symptoms, body weight, blood pressure, plasma concentration and renal excretion of electrolytes (*patients D.B.* and *D.L.*) were observed. To control the possible psychological effect of discontinuing and resuming treatment, injections of sesame oil were substituted for injections of hormone during the control periods.

symptoms of diabetes insipidus in this patient (fig. 1). On this regimen the 24-hour urine volume varied between 6,000 and 9,000 cc. A dose of aqueous posterior pituitary extract 0.2 cc. or larger could not be given without inducing intestinal cramps and nausea.

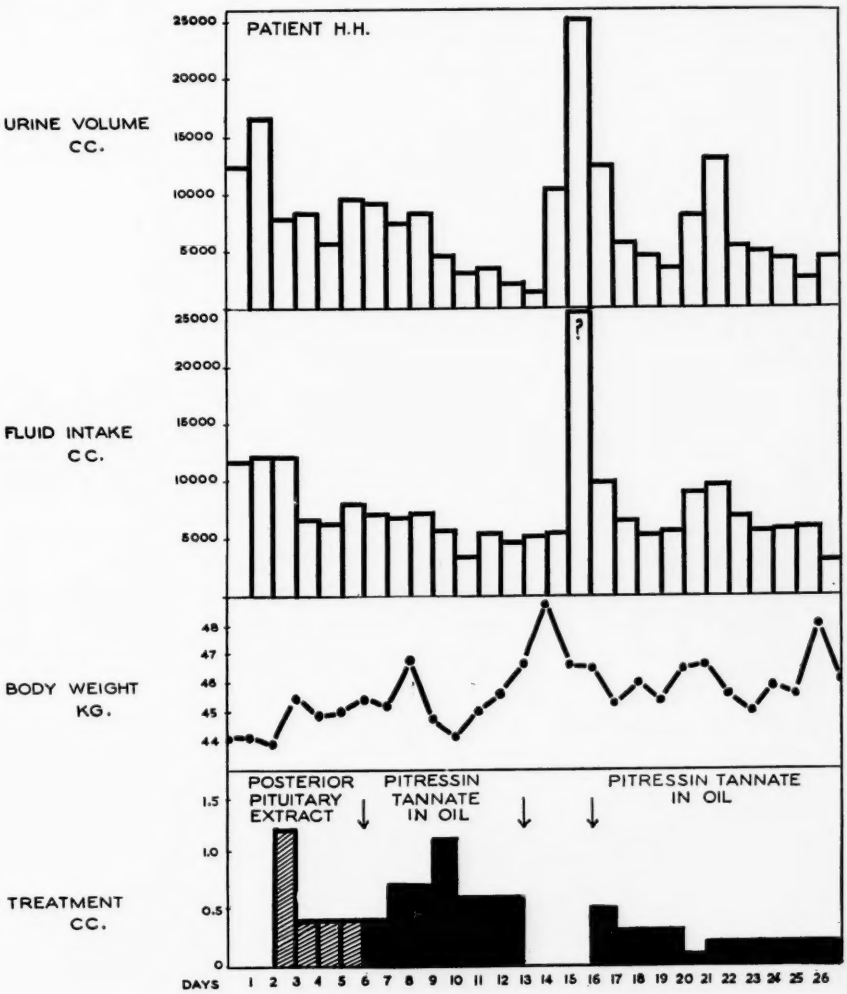


Fig. 1. Graph of data on *patient H.H.*, diabetes insipidus. Therapy with posterior pituitary preparations.

OBSERVATIONS

*Patient H.H.* During a preliminary period of study it was noted that 0.1 cc. of aqueous posterior pituitary extract, injected subcutaneously every 4 to 6 hours, was necessary to ameliorate the signs and

When pitressin tannate in oil was substituted for the injections of aqueous extract, a comparable dose (0.1 cc. administered intramuscularly every 6 hours) was given. Since this dose did not immediately prove to be more effective than treatment with aqueous extract, the dose of hormone in oil was increased (fig. 1). Subsequent experience indicated that it re-

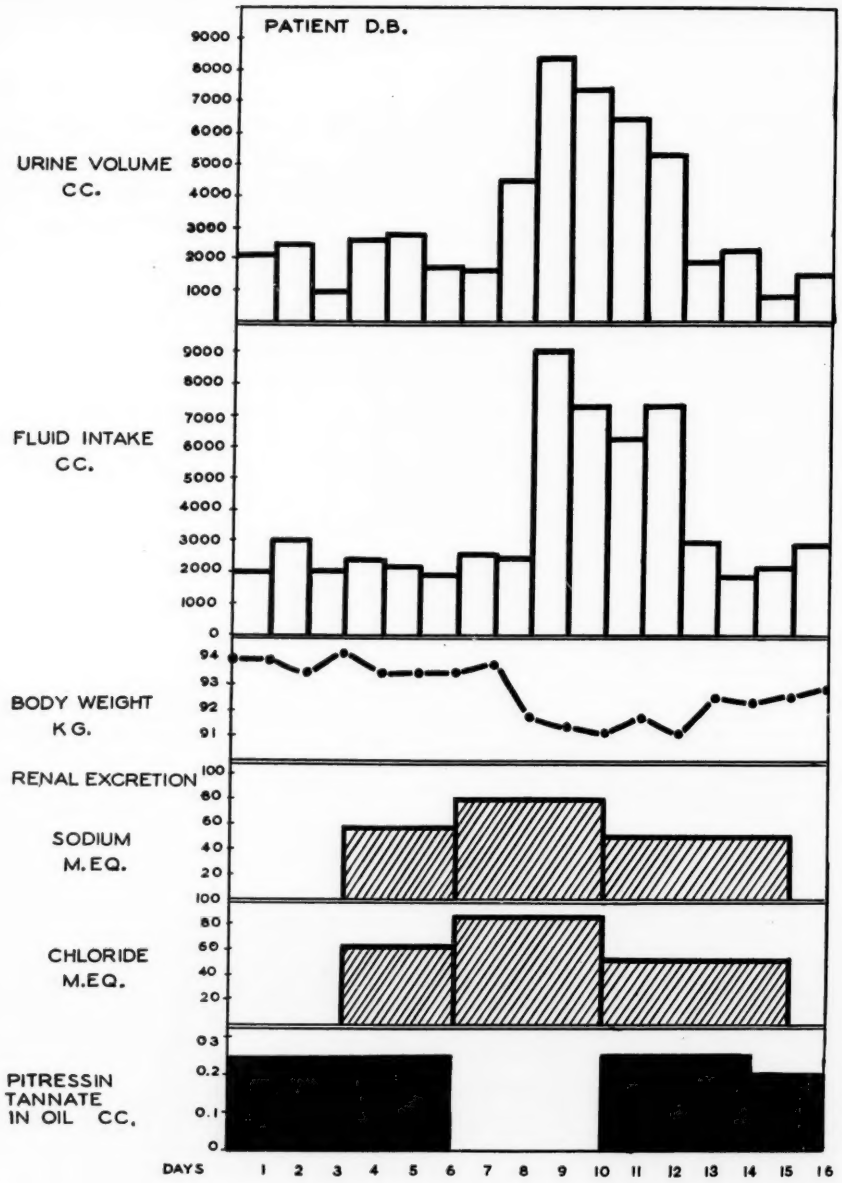


Fig. 2. Graph of data on *patient D.B.*, diabetes insipidus. Therapy with pitressin tannate in oil. The patient was maintained on a constant mineral intake throughout the study.

quired 48 to 72 hours to attain the maximum effect from any particular dose-level and that the increase in the dose of pitressin tannate in oil was entirely unnecessary in the case of this patient since the maintenance dose of hormone was ultimately determined to be a single, daily injection of 0.2 cc. On this regimen the 24-hour urine volume fluctuated between 2,700 to 5,600 cc. and the symptoms of polydypsia were completely controlled.

It was of considerable interest to observe that following the injection of a single dose of 0.5 to 0.7 cc. of pitressin tannate in oil, the patient experienced no

intestinal cramps, nausea or other untoward symptoms which had invariably followed the injection of much smaller quantities (0.2–0.3 cc.) of aqueous extract. This finding suggested that a high concentration of hormone was not present at any time in the circulating body fluids following the intramuscular administration of this quantity of hormone in oil.

The prolonged effect (48 hours) of a single injection of hormone in oil was noted on repeated occasions. Some indication of this effect is apparent from the fact that during the second 24-hour period following the withdrawal of pitressin tannate therapy (fig. 1) the urine volume amounted to only 1,600 cc. During the subsequent 48 hours, in the continued absence of therapy, the volume increased rapidly to a maximum of 25,300 cc.

From the studies on *patient H.H.* it appeared that, in comparison to treatment with aqueous extract, much larger quantities of hormone in oil could be tolerated without the appearance of intestinal cramps and nausea, that it required 48 to 72 hours to attain the maximum effect from any particular dose-level, that a somewhat larger-than-maintenance dose was required if immediate regulation was desired, that it was possible to obtain fairly satisfactory control of symptoms by administering the hormone at 48-hour intervals, provided a dose somewhat larger than the daily maintenance dose was given, and that the administration of excessive doses of hormone in oil were accompanied by oliguria, water retention, rapid gain in weight, headache, restlessness and drowsiness.

TABLE 1. CHANGES IN BLOOD CHEMISTRY WHICH WERE OBSERVED IN RELATION TO PITRESSIN TANNATE IN OIL THERAPY (*patient D. B.*)[1]

| Clinical state | Duration of therapy | Dose of pitressin tannate in oil | Body weight | Hematocrit (% volume packed cells) | Total serum protein gm./100 cc. | Serum sodium m.eq./l. | Serum chloride m.eq./l. | Serum $CO_2$ combining power m.eq./l. | Serum potassium m.eq./l. | N.P.N. mg./100. cc. | Glucose | Plasma volume | % Expected normal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *days* | *cc.* | *kg.* | | | | | | | | | *cc.* | |
| Treatment | 10 | 0.25 | 93.5 | 42.4 | 5.9 | 135.8 | 101.0 | 27.1 | 4.1 | 30 | 95 | 3030 | 126 |
| No Treatment | 4 | 0 | 91.1 | 44.0 | 6.3 | 148.6 | 106.6 | 27.8 | 4.4 | 21 | | | |
| Treatment | 5 | 0.25 | 92.5 | 43.0 | 6.2 | 144.3 | 103.6 | 25.0 | 6.0 | 24 | | | |

[1] During these studies the patient was provided with a diet of constant mineral content.

Following the daily administration of 0.6 cc. of pitressin in oil for a period of three days (fig. 1), oliguria and excessive water retention were noted. A rapid gain in weight (approximately 2 kg.) within 24 hours was associated with headache, restlessness and drowsiness. These symptoms persisted for 36 to 48 hours after the last injection of hormone.

Upon discharge from hospital, *patient H.H.* was instructed to take a single daily intramuscular injection of 0.10 to 0.20 cc. of pitressin tannate in oil. On this regimen her symptoms have been well controlled for a period of eight months. Polydypsia has not recurred and the 24-hour urine volume fluctuates between 2,500 and 4,500 cc. Nocturia, which previously had been very distressing, no longer is present. With the exception of an appreciable increase in the amount and duration of menstrual flow, no untoward symptoms from therapy have been noted. Recently a single injection of 0.20 to 0.30 cc. of hormone in oil every 48 hours has been substituted successfully for the daily injection. The moderate increase in night urine volume which occurred on this regimen during the second night of the 48-hour period has been prevented to a large extent by administering the hormone in the evening rather than in the morning.

*Patient D.B.* This patient had not received posterior pituitary extract therapy prior to this study. Satisfactory regulation of her symptoms was accomplished by administering a single daily injection of 0.25 cc. of pitressin tannate in oil (fig. 2). On this regimen polydypsia disappeared and the 24-hour urine volume fluctuated between 1,700 and 3,000 cc. When therapy was withheld for four days polydypsia recurred, the 24-hour urine volume increased to 7,000 to 8,000 cc. and the patient lost weight (2.7 kg.). Resumption of therapy (0.25 cc. daily) again was followed by the disappearance of polydypsia and polyuria and the patient gained weight. It is of interest to note that when only 0.25 cc. of hormone was administered once daily during the recovery period, a normal urine volume was not attained until the third successive day of therapy. Subsequently it was observed that a daily maintenance dose of 0.15 cc. was adequate. On this regimen her signs and symptoms of diabetes insipidus have been well controlled for a period of seven months.

The renal excretion of sodium and chloride was decreased by pitressin tannate therapy (fig. 2). When hormone therapy was withheld the daily excretion of sodium increased from an average value of 58.2

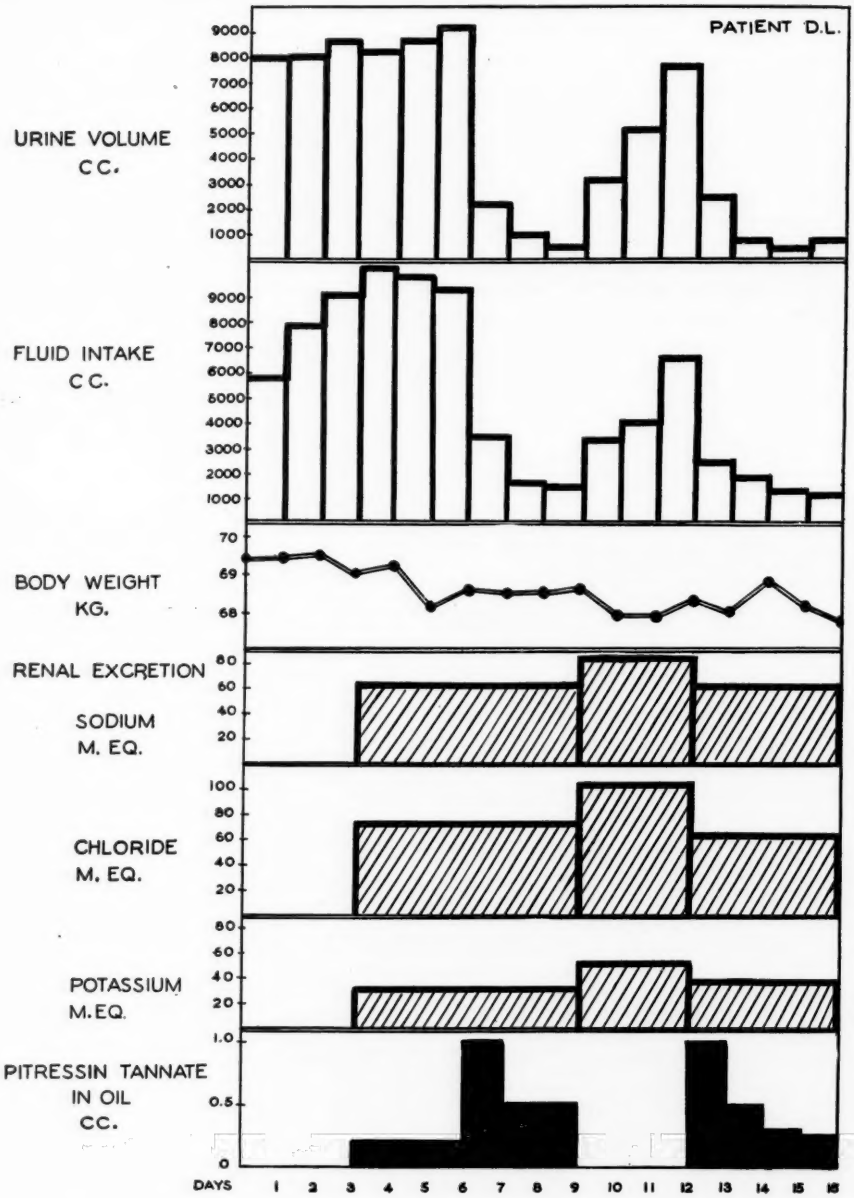


Fig. 3. Graph of data on *patient D.L.*, diabetes insipidus. Therapy with pitressin tannate in oil. The patient was maintained on a constant mineral intake throughout the study.

m. eq. to 80.0 m. eq. per day and the chloride excretion increased from a level of 62.9 m. eq. to 83.8 m. eq. per day. Resumption of hormone therapy was followed by a decrease in the excretion of sodium from 80.0 m. eq. to a level of 50.2 m. eq. and chloride from 83.8 m. eq. to 50.3 m. eq. per day.

The changes in blood chemistry which were observed in relation to the changes in renal excretion are given in table 1. The withdrawal of hormone therapy was followed by a striking rise in the serum concentration of sodium, and to a less extent chloride, despite the increased renal excretion of these electro-

lytes. That these changes were not due to hemoconcentration was indicated by the very slight rise in the volume of packed red cells (hematocrit) and serum protein level which occurred during this period. The marked diuresis which occurred when therapy was withheld and which was accompanied by an increase in the serum concentration of sodium and chloride despite an increase in the renal excretion of these substances, suggests that during this period water was lost in considerable excess over sodium and chloride. This further suggests that the dose of hormone during the previous period of therapy had been somewhat larger than necessary and had resulted in excessive water retention.

Five days after treatment had been resumed, blood studies indicated that a slight decrease in the serum concentration of sodium and chloride had occurred. The fact that these values did not reach those which were attained during the initial period of therapy may be due to the much shorter period of therapy in the second instance.

The plasma volume of this patient was found to be 3,030 cc., 126% of expected normal (method of Gregersen and Gibson, using the dye T-1824) during therapy. From a study of the relatively slight changes in hematocrit it would appear that the plasma volume fluctuated only slightly in relation to the tremendous shifts in total body fluid.

*Patient D.L.* During a control period the 24-hour urine volume of this patient amounted to approximately 8,000 cc. (fig. 3). No improvement in polydypsia or polyuria was observed during the first three days of pitressin tannate therapy (0.2 cc. daily). At this time larger quantities of hormone were given, 1.0, 0.5 and 0.5 cc. respectively on three successive days. The increased dose of hormone was followed by the disappearance of polydypsia and by a reduction in urine volume to 560 cc. At this time hormone therapy was discontinued and the urine volume subsequently increased to approximately 8,000 cc. on the third day without treatment. At this time resumption of treatment (1.0, 0.5, 0.3 and 0.25 cc. respectively) was accompanied by a prompt disappearance of polydypsia and by oliguria. In this instance the immediate effectiveness of a single large daily dose of hormone in oil (1.0 cc.) was demonstrated by a striking reduction in urine volume during the first 24 hours of treatment. Subsequently this patient was regulated very well by means of a single daily dose of 0.20 cc. of pitressin tannate in oil. This treatment has now been continued successfully for a period of 6 months. The daily urine volume amounts to 2,000 to 2,500 cc.

Recently this patient observed a marked increase in the duration and amount of menstrual flow, so much so that it was necessary to discontinue temporarily the pitressin therapy during the last catamenia.

A study of the changes in renal excretion of electrolytes in relation to pitressin therapy was also made in this patient. During pitressin therapy the renal excretion of sodium amounted to 63.8 m. eq. daily. When hormone therapy was withdrawn for three days there was a striking increase in the excretion of sodium to 85.4 m. eq. per day. Resumption of therapy was followed by a reduction in sodium excretion to 61.5 m. eq. per day. Changes in chloride excretion paralleled those of sodium, and the effect of hormone on the renal excretion of these electrolytes was very similar to that which was observed in *patient D.B.* Potassium excretion was also increased appreciably following the withdrawal of hormone therapy. The excretion of inorganic phosphorus and total nitrogen decreased throughout the experiment. These latter changes were probably due to the fact that the caloric content of the constant diet was somewhat below maintenance for this patient. Evidence of this is apparent in the slight but continued weight loss throughout the balance study.

## DISCUSSION

From a study of these three patients it appeared that a dose of more than 0.25 to 0.30 cc. of pitressin tannate in oil daily should not be continued unless the clinical condition of the patient is being followed closely. A correspondingly larger dose may be given safely when treatment is administered only once in 48 hours. It seems quite probable that many patients may be treated satisfactorily by a single injection of hormone every 48 hours, although more complete control of polydypsia and polyuria is obtained when the hormone is given once daily.

Because pitressin tannate settles out of the oil solution rather readily, it is well to instruct patients to shake vigorously the contents of the ampule or vial before the solution is withdrawn. On two occasions the supposed ineffectiveness of the hormone was shown to be due to the fact that the ampule of pitressin tannate in oil had not been shaken sufficiently before the solution was used.

No toxic effects have been observed in conjunction with pitressin tannate therapy other than those of water intoxication which follow the continued administration of excessive doses of hormone. The effect of pitressin therapy in increasing the amount and duration of menstrual flow necessitated its temporary withdrawal during catamenia in one patient.

The study of the effect of pitressin tannate in oil on the renal excretion of sodium and chloride in *patients D.B.* and *D.L.* indicated that the excretion of these electrolytes was decreased during the period of hormone therapy. These observations confirm the

studies which have been made on the action of pituitrin by Weir et al. (12) and by Lavietes et al. (13).


## SUMMARY

A single intramuscular injection of pitressin tannate in oil was very effective in controlling polydypsia and polyuria for a period of 24 to 48 hours in 3 patients with diabetes insipidus.

The maximum therapeutic effect from any particular dose level was not attained for 48 to 96 hours. For immediate control of symptoms a dose considerably larger than the maintenance dose was required. The continued administration of excessive quantities of pitressin tannate in oil resulted in the appearance of signs and symptoms of water intoxication.

In two patients the administration of pitressin tannate in oil increased appreciably the amount and duration of menstrual flow.

Mineral balance studies indicated that the renal excretion of sodium and chloride was reduced during periods of pitressin therapy.


## CONCLUSION

Pitressin tannate in oil was very effective in the treatment of three patients with diabetes insipidus. The intramuscular injection of a relatively small quantity of pitressin tannate in oil at intervals of 24 to 48 hours effectively controlled the polydypsia and polyuria of these patients. The renal excretion of sodium and chloride was decreased during periods of pitressin therapy.

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## PROTOCOL

*Patient H.H.* (*No.* 198067) a white female, 36 years of age, was admitted to the Johns Hopkins Hospital on April 14, 1940, complaining of marked thirst and increased urinary output. She had been quite well up to 1932 when she became aware of increasing thirst, urinary frequency and a greatly increased urinary output. In 1938 by charting her intake and output, the patient noted that at times her urine volume amounted to as much as 24 liters during a 24-hour period. It was never less than 12 to 14 liters per day. At this time (1938) she weighed approximately 55 kg., weakness developed and her appetite began to fail. During the summer of 1939 she was given 1 cc. of pituitrin, intramuscularly, daily. This treatment resulted in considerable relief of her thirst and urinary frequency but was associated with abdominal cramps and diarrhea. In August 1939 her treatment was changed to powdered pituitary extract insufflation. However, this resulted in considerable local nasal irritation and gastric distress and subsequently had to be discontinued. The patient states that this latter form of administration did control her symptoms of polydypsia and polyuria exceedingly well. From October 1939 until April 1940 she received 1 cc. of pituitrin 3 or 4 times daily, depending upon her needs. During this period she lost 13 kg. and the injections were accompanied by abdominal cramps, tremulousness, weakness, pallor, occasional fainting and menorrhagia. During her first hospital admission in April 1940 it was observed that satisfactory regulation of water balance could be accomplished by administering 0.3 to 0.5 cc. of pituitrin 4 to 6 times daily by injection. The patient was maintained on this therapy from April 1940 to November 1940 at which time she was readmitted for pitressin tannate in oil therapy because of her continued sensitiveness to even small doses of pituitrin and because of the practical difficulty associated with giving subcutaneous injections 4 to 6 times daily.

At 4 years of age the patient had had pneumonia. There was no history of other childhood infections. Her appendix was removed in 1924 and the tonsils in 1932. Between 1934 and 1937 she had had several attacks of "neuritis." Each was associated with fever of 100 to 103°F., with severe pain in the neck, shoulders and arms, with numbness and tingling in the fingertips. There was severe pain in these joints on motion but no redness or swelling. The attacks would last 1 to 2 weeks and subside promptly without residual changes. Her family history was noncontributory.

*Physical examination.* Physical examination (11-2-40) revealed a thin, somewhat underdeveloped woman with dry, flushed skin. Her temperature was 100.4°F., pulse rate 118, respirations 20, blood pressure 110/70 mm. of Hg and body weight 45.0 kg. With the exception of tachycardia, a slight systolic blow at the apex of the heart and a liver edge which could be palpated at the costal border, physical examination revealed no abnormalities.

*Laboratory examination.* R.B.C. 5.18 millions, Hb. 17.0 gm., hematocrit (volume % cells) 51.5, W.B.C. 7,600 with 80% polymorphonuclears. Blood chemical studies revealed the NPN to be 20 mg., the blood glucose 100 mg. and the serum proteins 5.50 gm. per 100 cc. The serum concentration of chloride was 92.4, the bicarbonate 29.1, sodium 120.6 and potassium 3.8 m.eq. per liter. Roentgenograms of the skull and sella turcica were reported as showing no abnormalities. The chest, heart and aorta were also normal. The stomach was somewhat hypertonic and

a small hiatus hernia in the cardiac end of the stomach was noted. The B.M.R. was 5% above standard. The urine was acid and clear, with a specific gravity of 1.003. The phenolsulphonphthalein excretion was 78% in two hours, with 55% excretion of the dye in the first ½ hour. The Wassermann reaction was negative. A tuberculin test (1:10,000) was positive at the end of 48 hours.

*Patient D.B.* (*No. 214421*) a white female housewife, 63 years of age, was admitted to the Johns Hopkins Hospital on November 2, 1940, complaining of dryness of her lips, tongue and throat, extreme thirst and increased urinary output. These symptoms were first noted during August 1940. From August 1940 until the time of her admission she had lost 11 kg. in weight and had become progressively weaker. Her past history revealed that she had had the usual childhood illnesses including measles, and that at age of 17 she had suffered an attack of typhoid fever without any known sequelae. She has 3 children, all alive and well. Her family history was non-contributory.

*Physical examination.* Physical examination revealed a well-developed, rather well-nourished elderly white woman who showed considerable evidence of recent weight loss. Her temperature was 99.6°F. (rectal), pulse rate 86, respirations 20, blood pressure 120/70 mm. of Hg, and body weight 93.5 kg. Her skin was dry, loose and inelastic. Examination of the eyes revealed no abnormalities in either the fundi or the visual fields. The tongue was dry and somewhat coated. The remainder of the physical examination revealed nothing of note.

*Laboratory examination.* The 24-hour urine volume approximated 6 liters, the specific gravity being 1.001 to 1.010. No sugar, albumin or formed elements were observed. The blood Wasserman reactionn was negative. The R.B.C. were 5.2 millions, the Hb. 14.6 grams, the hematocrit 42.4% cell volume and the W.B.C. 6,840 with 71% neutrophiles. Chemical analysis of the blood revealed the NPN to be 30 mg., the fasting blood glucose 95 mg., and the serum protein 6.35 gm. per 100 cc. of blood; the serum chloride 101.0, serum bicarbonate 27.1, serum sodium 135.8 and serum potassium 4.1 m. eq. per liter. Spinal fluid examination revealed nothing abnormal. Roentgenograms of the chest, skull and kidneys were normal. Tuberculin test was negative in a dilution of 1:100,000 but positive in 1:10,000. Venous pressure and circulation times (paraldehyde and sodium cyanide) were within normal values. The phenolsulphonphthalein test revealed 75% excretion of the dye in 2 hours, i.e., 25% in 15 min., 18% in the next 15 min., 20% in the next 30 min., and 12% in the last hour. The urea clearance was 88% of normal maximum clearance. The B.M.R. was 11% above standard. The skin resistance (Dr. Curt P. Richter) was normal (high palmar readings have been observed in patients with tumors of the third ventricle). The plasma volume, determined by the method of Gregersen and Gibson was 3,030 cc. (126% of expected normal).

*Patient D.L.* (*No. 217816*) a white girl, 13 years of age, was admitted to the Johns Hopkins Hospital on December 29, 1940, complaining of increased thirst and increased urinary output. She had been quite well until 1934 when polydypsia first appeared subsequent to a very mild attack of measles. During the preceding two months she had taken 1 cc. of Pituitrin (Squibb) at bed time which prevented the nocturia but did not affect the frequency throughout the day. Multiple injections of pituitrin throughout the day were necessary to keep the urinary output within normal limits and to control the thirst. With the exception of an attack of measles in 1934 which was very mild and not associated with any demonstrable neurological changes the past history was not remarkable. Menstruation began at the age of 12 and had been regular. The flow had been somewhat increased in both quantity and duration since the patient had been taking the pituitrin injections. Family history is negative except for the fact that both her father and brother are somewhat obese and the patient's mother has been taking thyroid medication for a menstrual disorder.

*Physical examination.* This revealed a well-developed, moderately obese, white school girl who was both pleasant and cooperative. Her temperature was 99°F. (rectal), pulse rate 80, respiration 20, and blood pressure 110/70 mm. of Hg and body weight 68.0 kg. Examination of the eyes revealed no abnormalities in visual fields and the fundi were clear. There was slight acne, particularly over the forehead. There was a moderate excess of weight across the shoulders, hips and thighs. The breasts were well developed and the external genitalia were normal in development. The fingers were tapering. No abnormalities were observed in the neurological examination and the remainder of the physical examination presented nothing of note.

*Laboratory examination.* The 24-hour urine volume approximated 8 liters under normal condition with a specific gravity of 1.003. No sugar, albumin or formed elements were noted. The blood Wassermann reaction was negative. The hematocrit was 40.6% cell volume and the W.B.C. 7,300 with 75% polymorphonuclears. Chemical analysis of the blood revealed the NPN to be 32 mg., the fasting blood glucose 94 mg., and the serum protein 7.0 gm. per 100 cc. of blood; the serum chloride 104.4, serum bicarbonate 27.5, serum sodium 142.6 and serum potassium 5.0 m. eq. per liter. Tuberculin test in both 1:10,000 and 1:1,000 dilution was negative. The B.M.R. was 4% below standard. Phenolsulphonphthalein test revealed a total excretion of 80% with 45% excretion of dye in the first 15 minutes. Roentgenograms of the renal pelves and skull revealed no abnormalities.

*Patient D.L.* was referred by Doctor Harriet G. Guild of the Department of Pediatrics, the Johns Hopkins University and *patient H.H.* was referred to our clinic by Doctor Harold H. Golz of Clarksburg, West Virginia.

# Simmonds' Disease with a Cranio-Pharyngioma

[Simmonds' Disease]

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THE MAJORITY of reported cases of Simmonds' disease have occurred among multiparous women. In these cases the cause is believed to be postpartum necrosis of the pituitary either following ischemia (1) or embolic infarction of the gland (2). It is of course known that any process which destroys or severely injures the anterior pituitary may produce this syndrome. Among the other causes ascribed are syphilis, tuberculosis, abscesses, inflammation and tumors. Only a relatively small number of proven cases of Simmonds' disease following destruction of the pituitary by a tumor have been reported. Whether this paucity of reports is a reliable index of the actual number of such cases is open to question. In our clinic only two patients with Simmonds' disease have been recognized and in both instances a pituitary tumor has been found. One of these cases has been reported (3). The present case has a striking similarity to the first.

### CASE REPORT

*F.B.*, a white unmarried female, aged 26, was admitted to the Edward J. Meyer Memorial Hospital on March 4, 1940, complaining of gradual impairment of vision and periodic headaches since 1932. Since 1938 the patient had polydipsia, polyuria and nocturia. During the year prior to admission she suffered anorexia and postprandial projectile emesis and had lost about 20 pounds in weight. The patient started school at about 7 years of age progressing only as far as the third grade. She attended a school for mental defectives from 1934 to 1938. Often the patient would sleep from 15 to 17 hours at a time. She was exceedingly fond of candy and sweet foods. She had never developed any secondary sex characteristics and had never menstruated. Libido was absent.

On examination the patient was found to be underdeveloped and poorly nourished and appeared about 12 to 15 years younger than the stated age (fig. 1). Her head was relatively large and the frontal bossae were prominent. There was an alternating exophoria, the patient preferring to fix with the right eye. There was also present both horizontal and vertical nystagmus although the movements were very slow. The temporal fields were restricted. The fundi showed optic atrophy with early venous engorgement. Vision was 20/200 O. S. and 20/70 O. D. The chest, heart and abdomen were normal. The blood pressure was 80 mm. Hg systolic and 60 mm. diastolic. The patient showed absence of all secondary sex characteristics. The breasts were atrophic, there was an infantile configuration of the external genitalia and complete absence of pubic and axillary hair. The extremities were normal. On neurological examination all the cranial nerves except the optic nerves were normal. There were no sensory or motor changes; there was no ataxia or dysmetria. Deep and superficial reflexes were active and equal. The skin was dry and wrinkled. The hair was coarse, a gray brown color on the scalp and sparse on the eyebrows and lashes. The patient weighed 76 pounds.

Body measurements were as follows: height 56 inches; crown to tip of acromium 7 inches; tip of acromium to tip of middle finger 24.5 inches; finger to finger 52.8 inches; crown to umbilicus 21.5 inches; crown to trochanter 26.5 inches; trochanter to feet (sole) 30 inches; top of knee cap to sole 16.5 inches; trochanter to top of knee cap 13.5 inches.

Laboratory and roentgen-ray studies gave results as follows. Blood chemistry: urea 13 mg.%; sugar 79 mg.%; serum cholesterol 258 mg.%. Urine analysis showed no abnormalities. The basal metabolic rate was −38%. The Wassermann reaction was negative. Serial blood counts showed a hypochromic, microcytic anemia. The white blood cells ranged from 3,500 to 5,900 per cc. A differential white cell count showed 60% polymorphonuclear leukocytes, 3% eosinophiles, 36% lymphocytes and 1% monocytes.

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A roentgenogram of the skull showed the floor of the sella turcica and the anterior clinoid processes to be completely destroyed. Some remnants of the posterior clinoid processes were present. The destruction seemed most likely due to a pituitary tumor which showed dense calcification of the capsule and was seen (fig. 2) to project upward and anteriorly for 6.5 cm. Roentgenograms of the spine, femurs, tibiae and fibulae taken in March, 1940, showed osteoporosis. The epiphyseal lines of the long bones were still persistent, indicating a delayed ossification.

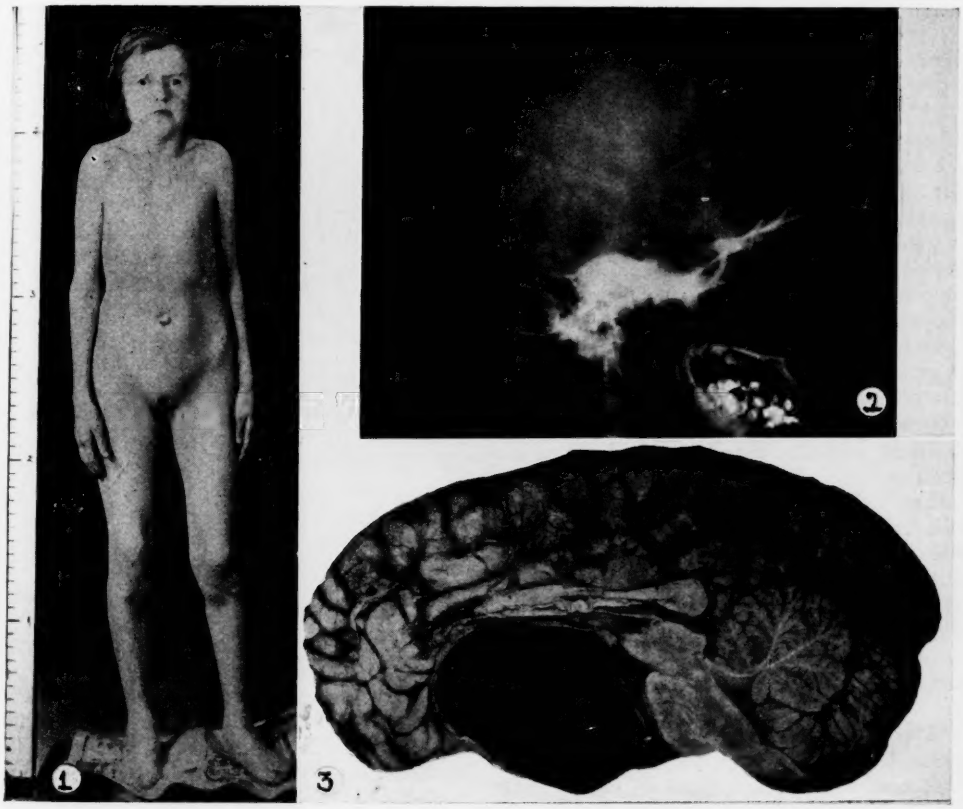

Fig. 1. Photograph of the patient. Fig. 2. X-ray of the skull. Note the dense outline of the tumor capsule and the enlarged sella turcica. Fig. 3. Photograph of the tumor.

The clinical course was unstable. At first the patient seemed content to lie in bed throughout the day, sleeping much of the time. She appeared apathetic and indifferent to her surroundings. Her appetite was poor. Her temperature ranged between 95° and 97°F., and the pulse rate from 50 to 72 per minute. Thyroid extract was then administered and within a few days there was a remarkable response producing a complete change in personality. The patient became active and energetic and began to play games. This, however, was only temporary for soon after she again appeared to be failing in health. Her weight at this time was 69¾ pounds, a loss of 6¾ pounds in the two months since admission. In May 16, 1940 an exploratory craniotomy was performed and an inoperable calcified suprasellar tumor was found. Death occurred five days later. Postmortem examination was performed under the direction of Dr. William F. Jacobs.

*Autopsy findings.* The body was that of a slender, white female, very pale in appearance. The external genitalia were infantile, pubic and axillary hair were absent. There was no evidence of breast tissue. After removal of the calvarium clotted blood was found between the dura and the calvarium. The meninges were wet, the convolutions flattened, the sulci partially obliterated. On removal of the brain a large, globular, thick-walled, partially calcified mass was found occupying the site of the pituitary gland (fig.

3). This was roughly egg-shaped and measured 5.5 cm. in length by 4 cm. in its greatest width. The sella turcica was deepened and enlarged, measuring 3 cm. in diameter. Both the anterior and posterior clinoid processes were destroyed. The optic nerves were thinned to flat ribbon-like structures and were widely separated over the tumor mass. On cross section through the mid-portion of the brain and through the tumor mass, it was noted that the ventricles were not distended. The tumor was of a dark red to brown color, and somewhat gelatinoid and granular in consistency. It was surrounded by a thick capsule which in some portions seemed completely calcified or ossified.

A moderate pulmonary congestion was present. A small remnant of the thymus gland was found. The heart, lungs, pancreas, spleen, kidneys, adrenals, ovaries, urinary bladder, fallopian tubes and uterus were normal in appearance and relations, but were atrophic and definitely reduced in size. The adrenals were found with difficulty because of their small size. The kidneys showed fetal lobulations. The combined weight of the lungs was 745 gm., the heart weighed 165 gm., the spleen 92 gm., the liver 696 gm., the kidneys together 122 gm. and the thyroid 13 gm.

*Microscopic findings.* Sections of the tumor through the capsule showed a dense, hyalinized, fibrous-like stroma containing distinct spicules of bone and scattered masses of brownish pigment. In certain areas collections of small round cells, monocytes and cellular debris were seen. Some areas showed shadowy outlines of ganglion-like cells with vesicular nuclei while other areas contained columnar cells that varied in height and seemed to have partly lost their cytoplasmic content and nuclear staining. Some sections showed numerous cholesterin crystals with giant cells. The main tumor mass appeared cystic and contained a homogeneous, structureless, colloidal acidophilic substance. Peripherally, the contents revealed vague outlines of cells and cellular debris. Other areas showed cleft-like spaces simulating vascular channels and some of these contained brownish pigment.

Sections of the thyroid showed thin flattened lining cells and colloid of varying density. The thymus appeared atrophic and infiltrated with fat. The lungs showed considerable edema. The liver, spleen and pancreas were essentially normal. The kidneys showed passive congestion. Sections of the adrenals showed a well stained cortex and medulla. Sections of the ovary showed a few Graafian follicles. The lining cells of the follicles consisted of a thin layer of flattened squamous cells. No ova were seen. A granular amorphous material was found within some of the follicles. Anatomical diagnosis: pituitary stalk tumor (craniopharyngioma); microsplanchnia; pulmonary edema; craniotomy.

## DISCUSSION AND SUMMARY

In the case reported the positive findings include retarded growth, polydipsia and polyuria, mental retardation, hypotension, impaired vision and ocular disturbances, dry skin, pathological sleep, depressed basal metabolism with hypopyrexia, and absence of secondary sex characteristics including atrophic breasts and genitalia as well as absence of axillary and pubic hair. This rather varied clinical picture certainly suggests a polyglandular syndrome with evidence of diminished or absent secretion of the growth, gonadotropic, thyrotropic and adrenotropic hormones of the pituitary. The impaired vision and ocular disturbances, hypersomnolence, hypothermia, polydipsia and polyuria and mental retardation suggest pressure on the optic chiasm and on the neighboring hypothalamic area of the brain. Of considerable interest in this case is the absence of cachexia as seen in the photographs of the patient. Evidently cachexia appears late in the Simmonds' syndrome. This point is perhaps worthy of some emphasis. It is perhaps of interest also that instances of Simmonds' disease following destruction of the pituitary by a craniopharyngioma may appear fairly early in life since these tumors are congenital in nature. The two cases from our clinic illustrate this point. In both cases pressure by the tumor on vital surrounding structures slowly destroyed the life of the patient and in both the tumor was found to be inoperable. Postmortem examination showed the microsplanchnia originally described by Simmonds, with marked reduction in size of all the internal organs. The pituitary tumor was a craniopharyngioma (Erdheim tumor) arising from embryonic rests of the original pituitary duct or stalk. (4). Cystic degeneration had occurred and the capsule of the tumor was infiltrated with bone.

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# Contributions from the United States of America to Endocrinology[1]

[Address]

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AS A REPRESENTATIVE of the United States of America to the Second Pan-American Congress on Endocrinology I have been asked to review the more important contributions which have been made in the United States. Although we are proud of the record already made, we recognize that there is far more still to be accomplished. Let nothing I say be understood as claiming the science of endocrinology for the United States. When we examine the earlier stages of any phase of this study we encounter the names of many eminent investigators from other countries. In the recent past as well as the present we recognize the invaluable participation of endocrinologists from many lands. For those of us who work in North America it is a welcome privilege to meet with you who have published so many excellent studies under such internationally known leaders as Professors Houssay, Lipschütz, Martins, and Mussio Fournier. Much of the work I shall mention as done in the United States could not have been accomplished without the previous discoveries made by these renowned men and their associates.

Endocrinology has developed as a branch of the spreading tree of medical sciences within less than a century. The pioneer discoveries of the pancreatic basis for diabetes by von Mering and Minkowski in 1889 and of thyroid therapy for relief of myxedema by Murray in 1891 mark the period of intensive experimental endocrinology as essentially the past 50 years. Although several of the more fundamental observations were reported from English and German laboratories the clinical and experimental contributions from the investigators in the United States represent a significant fraction of the endocrine accomplishment of this half century. It is interesting to trace rapidly some of the paths by which the work of one investigator has stimulated that of others in this endeavor which has enlisted so many zealous devotees of endocrine research.

The pioneer studies of apparatus for measuring metabolism in animals and men by Voit and Rubner in Germany laid the basis for Magnus-Levy's work which proved that metabolism was increased in thyrotoxicosis, decreased in myxedema. Pupils of these masters included Graham Lusk, who gave many years to the department of physiology at Cornell Medical School in New York City, and Francis Benedict, who spent the major part of his career in the Carnegie Institution Laboratory for Nutrition in Boston, Massachusetts. From these two American centers were developed a series of trained students of metabolism such as Eugene Dubois, Joseph Aub, Thorne Carpenter, Walter Boothby, and numerous others who have laid the foundations for extensive study of the diagnosis and treatment of thyroid disease. One of the most significant products of this work has been the construction of statistical bases for prediction of the heat production by the healthy human body, when age, sex, height and weight are specified. Subsequent and analogous studies by other authors from the United States and from European countries have served to improve the predictions by providing further data for the statistical methods.

The discovery of iodine as the unique element in the thyroid secretion by Kocher and Bauman in Switzerland and Germany soon led to the long series of studies by David Marine and his associates in the United States, which have contributed the fundamentals to our knowledge of iodine physiology. Whereas much remains to be found out, we know that iodine deficiency leads to goitrous enlargement of the thyroid, and iodine therapy during youth can prevent or cure such goiter. The demonstration of the practical way in which this knowledge can be used socially is due to Marine and his pupils, as well as to the Swiss workers, leading to the growing popularity of iodine containing salt for domestic use, and to the wide application of iodine in small weekly doses to the school population in many sections of the United States and in Switzerland. The incidence of goiter has been markedly reduced in those large geographic

[1] Presented before the Second Pan-American Congress on Endocrinology, Montevideo, Uruguay, March 5, 1941.

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areas where iodine content of soil and water is low. More recently other aspects of the physiology of iodine have been approached by several chemists and experimentally minded surgeons. Their studies of changes in blood iodine concentration hold some promise of diagnostic help in the questionable cases of thyrotoxicosis, but what is probably even more important, they may reveal methods for prevention and more rational treatment of the disorders of the thyroid.

The surgical extirpation of goiter, in which Theodore Kocher was a pioneer, became a problem of large importance in the region of the United States about the Great Lakes. In this area there grew up within the early years of the twentieth century an unusual clinical organization, the Mayo Clinic. Thyroidectomy was an urgent problem, with a disturbing mortality. The surgeons led by the brothers, William and Charles Mayo, had the fortunate cooperation of Henry S. Plummer, an internist, who revived the use of iodine as a means for temporarily reducing the toxicity of thyrotoxicosis and thereby diminishing the mortality from thyroidectomy. This step has revolutionized the practice of goiter surgery the world over. Many other steps have followed, such as carbohydrate and vitamin therapy to give greater protection to the liver in this treacherous disease. The technical methods of diagnosis, and more particularly of medical preparation for operation, minute details of surgical technic, and proper postoperative care have been elaborated with gratifying success in the two decades since Plummer's discovery, leading to a number of clinics in which there are highly specialized and successful teams for the treatment of thyrotoxicosis.

Exactly parallel in point of time there was an intensive study of all varieties of thyroid disease undertaken in Boston, at the Massachusetts General Hospital by James H. Means, as a consequence of which there have been a number of productive younger men graduated into this field within the past decade. From their work has come the realization that clinical effects from administered thyroid persist for 2 to 3 months after therapy is stopped. The clinical dependability of thyroidea sicca in myxedema has been demonstrated, and use of pure thyroxin shown to have no advantages. In general thyroid preparations have been found potent in proportion to iodine content. In recent years, Salter of this group, has been responsible for the demonstration that iodine can be made to unite with certain proteins in vitro, with production of artificial hormone-like substances. It is too early to tell what far-reaching results may come from such discoveries.

Although the experimental and clinical literature on thyroid is already more extensive than on any other endocrine gland, the number of investigators still occupied in this field in the United States is too large to allow enumeration here. It gives evidence of the active interest in the problems involved, and of the opportunities which constantly improving research tools afford to attack the unsettled questions.

### PARATHYROIDS

The studies of several North American investigators have pointed with increasing certainty to the probability that the parathyroids produce an internal secretion which maintains the normal level of blood calcium. This was climaxed in 1924 by Adolph Hanson's preparation of a parathyroid extract which could be used clinically for relief of parathyroid tetany. As a consequence three pharmaceutical manufacturers in the United States have been supplying a carefully standardized parathyroid extract which has been helpful in this distressing although uncommon malady.

Almost coincident with the discovery of the parathyroid extract Mandl, in New York, completed the proof that hyperfunction of these glands was the cause of the osteitis fibrosa cystica described by von Recklinghausen. Certain other aspects of calcium metabolism were being studied by Aub and Fuller Albright, in Boston. They proceeded with conspicuous success to the more exact description of the biochemical processes which are involved in decreased or increased parathyroid activity. Hyperfunction of the parathyroids has been shown to impair renal function if it is long continued. The excessive phosphorus excretion causes profound disturbances of nerve and muscle metabolism. The use of blood and urine estimations of calcium for early diagnosis has been placed on a sure foundation. The study of parathyroid pathology carried on by W. G. MacCallum, at the Johns Hopkins Hospital in Baltimore, led to the work by Fuller Albright, Read Ellsworth and D. H. Shelling as well as the improved dietary management of parathyroid diseases. The investigation of mineral metabolism in several other clinical laboratories has aided in understanding how calcium absorption is facilitated by adequate amounts of vitamin D. The relationship between ionized calcium and serum protein has been worked out with exactness. When, therefore, discovery of dihydrotachysterol was announced by Holtz, from Berlin, there were several clinics in the United States ready to apply the new hormone substitute with critical care, and to give it a dependable status in treatment of tetany during the past five years.

### POSTERIOR PITUITARY

The preparation of purified and concentrated extracts of the posterior lobe of the hypophysis depends

on the researches of John J. Abel and E. M. K. Geiling, at Baltimore, following the earlier English discoveries of the pressor and oxytocic activities of this gland. Among the more significant further investigations have been those by Oliver Kamm and his associates in the Parke, Davis laboratory showing the presence of separable oxytocic and pressor hormones. The puzzling variety of lesions which have been associated with diabetes insipidus has been explained, largely through the work of Ranson and his group, at Northwestern University. They have shown that destruction of the supraoptic nuclei in the hypothalamus, interruption of the fiber tracts running down from these nuclei through the infundibulum, or destruction of the posterior lobe of the hypophysis give similar results. This work has led to the concept of the 'neurohypophysis.' Important clinical applications of these discoveries made in the United States include the use of extracts or even crude powdered glands via the nasal mucosa, for relief from diabetes insipidus, or in stimulation of the postpartum uterus to firm contraction.

### ADRENAL MEDULLA

Some years after the discovery by Oliver and Schaefer in England of the pressor effects of adrenal gland extracts, there occurred the first isolation and synthesis of a hormone, epinephrine, accomplished by Abel in the Johns Hopkins University laboratories. During the 40 years since that time a voluminous literature has appeared, especially in the United States, concerning the relationship between this hormone and the activity of the autonomic nervous system. Walter B. Cannon at Harvard University is the leader of the group who believe epinephrine is secreted for emergencies when nervous stimulation increases adrenal activity. This position is disputed by J. M. Rogoff, who, with Gary N. Stewart, in Cleveland, has long maintained that the hormone is being continuously produced. The ramifications of these studies have included the discovery of other chemical substances, such as sympathin, liberated at the synapses of certain nerves.

### ADRENAL CORTEX

Another aspect of the intensive study of the adrenal glands was the attempt in many laboratories to prepare extracts which would act as an adequate substitute for the indispensable cortical tissue. Success was reported almost simultaneously from two laboratories by Frank Hartman at Columbus and Stewart and Rogoff at Cleveland. Numerous others have participated in the subsequent 14 years of intensive study of methods for preparing and standardizing adrenal cortical extracts. Several active steroid molecules have been identified in these preparations. Although the discovery of desoxycorticosterone and its synthesis by Reichstein in Switzerland led to enthusiastic use of this pure compound as a substitute for adrenal gland extracts by many clinicians, this is not the final answer to the clinical need. The work in several laboratories and clinics shows conclusively that there are several functions of the adrenal glands, such as the retention of sodium, control of the volume of circulating blood, the conversion of amino acid to glucose in the liver, and resistance to toxic materials. The maintenance of life as well as the physical strength and ability to withstand infections are dependent on adrenal cortex integrity and may well be related to the simpler physiological functions named. Clarification of these adrenal questions is being provided by intensive work now under way in a number of research institutions from all parts of the United States. As one consequence there is now a much improved prognosis for those patients with Addison's disease in whom active tuberculosis is not immediately threatening. Elective surgery has become possible for such patients. As a further result of study by the Mayo Clinic group it has become possible to apply a test of the ability to withstand salt restriction plus diuresis in detecting relatively slight deficiencies of the adrenal cortex, thereby making available adrenal cortex therapy for clinical cases before the disease has become florid, or possibly dangerously advanced.

### PANCREAS

Following the discovery in Germany by von Mering and Minkowski that extirpation of the pancreas led to diabetes mellitus there were many attempts to prepare pancreatic extracts for amelioration of human diabetes. Success attended the labor of Banting and Best in Toronto, Canada, after which one pharmaceutical manufacturer in the United States and 18 selected clinics in various parts of the country investigated the new material in the clinical management of many patients. So satisfactorily was this undertaking correlated that within twenty months after the initial discovery had first been announced any physician in the United States could secure through the channels of the drug trade dependable insulin for his diabetic patients. More recently the fortunate discovery by Hagedorn in Denmark of the prolongation of insulin action by coupling it with protamine has been further improved by North American workers who have shown the advantages of zinc, now incorporated in protamine zinc insulin, and who have produced the zinc insulin crystals.

An unexpected by-product of this study of diabetes was the recognition by Seale Harris, of Birmingham, Alabama, of a new syndrome, due to hypoglycemia, and produced by oversecretion of insulin.

The various types of clinical hypoglycemia have come to occupy an important position in that group of disorders studied by either the endocrinologist, neurologist or psychiatrist. In the exploration of the spontaneously occurring types the American clinicians have made exceptional contributions.

Within the last few years Dragstedt in Chicago has shown that there is another fraction in pancreatic extracts, which will restore to the depancreatized animal the ability to use fat more like the normal. This substance, christened lipocaic, is still an unknown quantity in clinical diabetes, but difficulties in the adequate control of a few diabetics lead some clinicians to await eagerly the further study of this material by the Chicago investigators.

The understanding of diabetes mellitus has been further complicated by the amazing series of experiments carried out by the Argentine students under Professor Houssay. Building on this well authenticated foundation it has been shown by Cyril N. H. Long and his associates in the United States that much of the diabetogenic activity of the anterior pituitary is due to the activity of the adrenal cortex. This same group has also shown the existence of a further direct pituitary effect on muscular metabolism. It is still far from clear what this means for clinicians who are responsible for the treatment of diabetic patients. But for the physiologist it demonstrates anew the interdependence of the various endocrine glands.

### ANTERIOR PITUITARY AND GONADS

In this correlated group of glands of internal secretion the importance of the anterior hypophysis became increasingly evident, due in no small part to the clinical and laboratory studies of Harvey Cushing at Harvard. Herbert Evans has for many years been pursuing the study of this same gland at the University of California, where a succession of students have uncovered many of the fundamental principles of the pituitary control over growth, maturation and activity of the reproductive system, sustained action of the adrenal cortex and thyroid, and effects of the gland on mammary secretion and on carbohydrate metabolism. The publication of researches in this field of pituitary physiology has involved almost every laboratory of physiology, biochemistry and anatomy in the United States within the past twenty years. It would be impossible to list here all those who have contributed valuable work.

One of the most striking features of this rapid progress has been the free cooperation of these numerous investigators, made possible by a series of fortunate circumstances. A growing appreciation of biological research has made possible increased support for such study. Larger and larger numbers of young men and women have become fascinated by the adventure of endocrine research. When Stockard and Papanicolaou, at Cornell, published their now classical study of the vaginal epithelial cells as a measure of ovarian hormone activity in the guinea pig, Edgar Allen, at the University of Missouri, recognized a new tool by which he and Edward Doisy, at St. Louis, were able to isolate the estrogenic hormone of the ovaries. This new instrument for research, the microscopic study of stained cells from the vaginal mucosa, has been the key with which a large number of problems have been unlocked in the succeeding years. Several different estrogenic molecules have been identified, their structural formulae assigned, and then synthetic production accomplished. The estrogens have been shown to produce proliferation in the uterine and vaginal mucosae. The induction of menstruation by variations in the concentration of estrogens has been accepted as at least a partial explanation of this unique female function. Papanicolaou and Shorr extended their original observations on guinea pigs to a study of human female vaginal cells, and were able thereby to make roughly quantitative estimations of the estrogens acting in patients.

One of the most significant applications of this exact knowledge of estrogenic materials has been the establishment of definite standards of potency for the estrogens, and the consequent introduction into clinical therapy of ovarian hormones in dependable forms. The varied uses of such endocrine material extend from the cure of gonorrheal vaginitis in very young girls to the relief of the climacteric symptoms and even the restoration to comfort of senile women with atrophic vaginitis or painful or dangerous skin lesions on the external genitalia.

Previous to this, observations by Leo Loeb and other North American students of sex physiology had made it highly probable that the decidual and progestational changes in the endometrium were induced by a secretion of the corpus luteum. With the increasing clarification of ovarian action on the uterus, due to the results of investigators already mentioned and others such as Frederick Hisaw, then at Wisconsin, it became possible to study the corpus luteum quantitatively. George Corner and Willard Allen, at Rochester, New York, devised the test which has become the international standard for progesterone, the pure hormone concerned. With definite standards of purity and activity it has now become possible to put into clinical use this progestational hormone, and to reduce the risk of abortion in the first trimester for those women with a tendency to recurrence of this accident.

Investigation of testicular functions was not as easily undertaken, because of lack of a method for

measuring hormone activity in an intact animal. The anatomists working under the leadership of Carl Moore and the biochemists of Frederick C. Koch's group have made the University of Chicago a center for the exact study of testis action. Bioassay technics have been elaborated, which have made possible the synthetic work done in European laboratories, as well as the further study of the male animal and human patient. It is fitting that the therapeutic application of testosterone to the underdeveloped male human being should be carried on most intensively by Kenyon, also at Chicago.

Parallel to this new knowledge of the physiology and chemistry of the gonads has been a remarkable study of the gonadotropic action of the anterior pituitary. Simultaneous reports appeared from Zondek in Germany and Philip Smith, then in California. The dependence of ovaries and testes on sustained stimulation from the hypophysis is now commonplace knowledge. In the elucidation of this story fundamental tools were provided by Philip Smith, now at Columbia University, with improved technic of hypophysectomy, and the continued series of researches from his laboratory group in New York are among the most important steps in this story which is still being unfolded. Hisaw and Evans, with their respective associates have contributed in a friendly rivalry and debate, to the further understanding of this complicated relationship, in which there appear to be at least two gonadotropic factors. It is probable that within a very short time the combined efforts of several laboratories in the United States will make crystalline pure pituitary materials available for this study. Already crude but biologically standardized pituitary extracts have been put into clinical use in cases of reduced fertility and disorders of reproductive function. It is confidently expected that production of pure materials will greatly improve the benefits to be obtained in the human applications of this knowledge.

The control exerted by the pituitary over growth had been emphasized by Cushing's study of the human being, and this was extended by Evans and his group to the point where they report a crystalline pure growth producing hormone. Using even the crude products which have been available for the past few years it has become possible to increase the stature of dwarfs significantly in many cases. The pituitary stimulation of the mammary gland secretion post-partum has been the subject of intensive work by three groups in the United States, under Charles W. Turner, W. R. Lyons and Oscar Riddle. With many features of this relationship still unexplained, this is not yet a function of the pituitary which can be controlled in the clinic, except that it is now possible, as shown by numerous reports within the past two years, to inhibit lactation when this is an undesirable function.

### DIGESTIVE HORMONES

There are some endocrine controls of importance in the sequence of actions of the stomach, duodenum, pancreas and gall bladder. Whereas the original demonstration of secretin is credited to Starling the discovery of cholecystokinin, which causes gall bladder contractions, and of enterogastrone, which inhibits gastric emptying, are from the very productive laboratories of Andrew Ivy in Chicago. These studies are still in the physiological stage, but clinical diagnostic applications are being investigated at present.

In conclusion may I suggest that if the list of men and accomplishments seems long, this is not submitted with any desire to claim credit. Rather do we wish to acknowledge with gratitude the opportunities and facilities which the institutions of our country have made available. May the contributions of the United States be taken as a practical measure of the thanks we desire to express for the privilege we enjoy, of being enrolled with our friends from the other American republics, in this fascinating and forward moving occupation, endocrine research.

# *Abstracts of*
# CURRENT CLINICAL LITERATURE

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## ADRENALS

CORI, C. F., AND A. DEM. WELCH.

The adrenal medulla. *J.A.M.A.* 116: 2590. 1941.

The secretion of the adrenal medulla is discussed under the following headings: history, innervation, pharmacological action in correlation with comparatively similar chemical structures, formation of epinephrin, the hemodynamic and metabolic effects, and the therapeutic uses.—*C.P.*

KADIKOV, B. I.

The blood-sedimentation test in cases of deranged activity of the suprarenal capsule. *Bull. biol. et méd. expér. URSS* 6: 651. 1938.

With the appearance of the first symptoms of insufficiency, such as loss of weight or a slight drop in temperature, as well as during the period of pronounced symptoms, the sedimentation ratio decreases. Experimental infection of animals with tuberculosis by injection of cultures into the suprarenal capsule or the lungs was accompanied by an increase in the sedimentation. This was greater when injection was made into the suprarenal capsule even though the course of the disease in the 2 cases was the same but was nevertheless pronounced when injection was into the lung. It can therefore be concluded that the stimulation of the suprarenal capsule in tuberculosis is accompanied by a derangement of its function. Addison's disease is to be regarded not only as a result of the weakened function of the suprarenal but rather also as due to the abnormal character of the activity of this organ.—*M. G. Moore.*

KATZ, F., AND F. MAINZER.

Successful grafting of adrenal gland in a case of Addison's disease. *Brit. M. J.* 1: 617. 1941.

Only 5 reports of successful transplantation of adrenal glands in human beings were found in the literature, that is, in which the cases were undoubtedly Addison's disease and the results observed for 5 months to a year. This report adds a 6th case. The adrenal gland of a patient in the same blood group who had just died was grafted into the abdominal muscle of a patient with severe Addison's disease. Results observed for 15 months are excellent. Only under special exertion or during temporary infection is adrenal insufficiency noted The case history is fully given. 14 references.—*J. B. Paton.*

KENDALL, E. C.

The function of the adrenal cortex. *J.A.M.A.* 116: 2394. 1941.

The adrenal cortex is reviewed under the following headings: physiological activities, resistance of the cortex to physiological stress, standardization of extracts, and function of the cortical tissue. The adrenal cortex does not elaborate any single substance which can be ascribed as the vital hormone of this gland, but extracts contain a large number of closely related steroid derivatives which have specific effects.—*C.P.*

LEMERE, F.

Cortical extract for bromide intoxication. *J.A.M.A.* 116. 1941.

Lemere, in a letter to the editor, supports Gilman's contention of the uselessness of cortical extract in bromide poisoning with 5 negative case histories.—*C.P.*

LOEB, R. F.

Adrenal cortex insufficiency. *J.A.M.A.* 116: 2495. 1941.

Cortical insufficiency is discussed under the following headings: clinical picture, pathological physiology, and the treatment of adrenal cortical insufficiency.—*C.P.*

WINTERSTEINER, O.

The adrenogenital syndrome. *J.A.M.A.* 116: 2679. 1941.

This syndrome embraces in the broadest sense of the term all conditions in which the abnormal changes in the sexual sphere are referable to organic or functional disturbances in the adrenal cortex. The literature on the manufacture of estrogens and androgens by the normal and pathological adrenal cortex is thoroughly reviewed. The data indicate a potential availability rather than an active functional secretion of androgens and estrogens from the normal adrenal cortex.—*C.P.*

## ENDOCRINE GENERAL

ROSS, M., AND R. I. DORFMAN.

An abortifacient substance in human urines. *Cancer Research* 1: 158. 1941.

Protein-like substances were concentrated from urines of 6 men and 8 women by precipitation of the fresh urine

with 10% Na tungstate, dissolving in a 60% $Me_2CO$-4% $NH_4OH$ mixture and precipitating the desired fraction from this solution by increasing the concentration of $Me_2CO$ to about 80% and adding a few drops of AcOH. These concentrates were tested for abortifacient action by subcutaneous injection into pregnant albino mice. The urine concentrates of 7 patients suffering from cancer exerted some abortifacient action. Concentrates of urine from 3 normal men gave no evidence of abortifacient action. In the urine of the other normal man some abortifacient action was present. The urine of 3 non-cancerous, but otherwise ill, women showed as much evidence of abortifacient material as did that of the other patients. Egg albumin in a saline solution injected in larger doses by dry weight than those of urinary powders did not have the same action. In doses of 5 mg. a prolactin preparation (90% pure) did not interfere with pregnancy in mice. Three subcutaneous injections of 8 mg. each, however, caused resorption, and with doses of 10 mg. each there was both resorption and expulsion. Three daily subcutaneous injections of 10 mg. of peptone were followed by normal deliveries in 3 mice and premature expulsion in 3 others. Three doses of 5 mg. of peptone each did not interrupt pregnancy in 7 mice. Gonadotropic preparations in doses ranging from 3.75 to 25.0 rat units per day for 3 days, produced death of the fetuses and their retention in the uterus beyond the expected date of their delivery.—*F. Saunders.*

## GONADS

Abarbanel, A. R.

The effects of testosterone propionate, methyl testosterone, anhydro-oxy-progesterone and progesterone upon lactation in the nursing human being. *Am. J Obst. & Gynec.* 42: 110. 1941.

Thirty-six patients were studied; 50 served as controls. Conclusions were: The onset of adequate milk secretion was not affected by 200 to 300 mg. of testosterone propionate intramuscularly, 100 to 500 mg. of methyl testosterone orally, 100 to 500 mg. of anhydro-hydroxy-progesterone orally or 100 mg. of progesterone intramuscularly. Established lactation was not affected by 250 to 500 mg. of testosterone propionate intramuscularly, or of methyl testosterone or anhydro-hydroxy-progesterone orally or by 100 mg. of progesterone intramuscularly.—*E.C.H.*

Albright, F., Patricia H. Smith, and Anna M. Richardson.

Postmenopausal osteoporosis. *J.A.M.A.* 116: 2465. 1941.

A decreased retention of Ca occurs after the menopause which results in osteoporosis chiefly of the spine and pelvis. Since estrogen therapy results in an increased retention of Ca, this condition is termed postmenopausal osteoporosis. Of 42 patients under the age of 65 with generalized osteoporosis, 40 were women who had gone through the menopause and only 2 were men. There were no cases in women before the menopause.—*C.P.*

Bennett, M. J., and P. B. Russell, Jr.

Surgical correction of oligomenorrhea, menorrhagia and menopause by ovarian isoplastism. *South. Surgeon* 10: 154. 1941.

An attempt was made to correct functional menstrual disturbances by exchanging ovarian grafts from 2 women suffering from disorders of contrasting types, i.e., menorrhagia and oligomenorrhea. Patients who did not respond to other types of therapy were selected. The 2 partners were operated on in adjoining operating rooms on the same day and a portion of 1 ovary was reciprocally exchanged. Objective evidence of success of the operation was obtained from a study of vaginal smears. Eighty isoplants were made, with but 1 therapeutic failure and with no deaths. Five patients, sterile from 1 to 15 years, became pregnant following the operation; one of these was delivered by Caesarian section and a living graft was demonstrated. In some cases, improvement of an associated metabolic imbalance was noted. The authors emphasize that the following requirements must be met in choosing suitable partners for this procedure: (1) The patients must belong to the same blood group and must be cross-matched; (2) the characteristics of their ovarian dysfunction must be complementary and to the same degree; (3) the tissues must be free of any transferable disease.—*Doris Phelps.*

Bickers, W.

Induction of ovulation. *Virginia M. Monthly* 67: 760. 1940.

A number of women showing lack of a progesterone-like type of endometrium as shown by biopsy prior to menstruation, were treated with equine gonadotropin, which produced a normal glandular endometrium.—*R. J. Main.*

Brewer, J. I., and H. O. Jones.

A study of the corpora lutea and the endometriums in patients with uterine fibroids. *Am. J. Obst. & Gynec.* 41: 733. 1941.

Study was based upon a prearranged clinico-pathologic routine rather than upon the collection of accumulated specimens. A protocol was prepared at the time of operation of the uterine and ovarian findings, interpreted by reference to the checked menstrual history of the patient. Prompt fixation of tissues was done. When the gross and microscopic pathologic findings in 100 cases of fibromyomata were correlated with menstrual data and with other clinical and surgical findings, it was concluded that the ovarian and endometrial cycles were not significantly altered. The fibromyomata of these patients were associated with no evidence of excessive or unopposed estrogenic stimulation.—*E.C.H.*

Collett, M. E., F. W. Reed, L. Isaac, S. Rouse and E. Yeakel.

Estrin potency and basal metabolism. *Am. J. Obst. & Gynec.* 42: 93. 1941.

The study attempted to evaluate the potency of estrogens by their effects on B.M.R. Five panhysterectomized women, 30 to 42 years of age, were given varying doses

of estrone intramuscularly and of estrone and estriol orally. Relatively small doses of estrogen produced a larger rise or a smaller fall in B.M.R. than did larger doses given the same individual. Differences in potency of various estrogens given by different routes could be estimated by changes in B.M.R. Therefore, orally administered estriol was less potent, unit for unit, than estrone similarly given, which was only slightly less potent than when given by injection.—*E.C.H.*

DANNREUTHER, W. T.

The treatment of pelvic endometriosis. *Am. J. Obst. & Gynec.* 41: 461. 1941.

The author in the course of this article (a general one dealing with the cases of 115 women personally operated upon during the past 10 years) observed that the use of progesterone 'has apparently helped to keep some of these women comfortable.' G. V. S. Smith, in discussion of the paper, questioned the rationale of giving progesterone and suggested that testosterone might prove more effective in producing temporary inactivity of the ovary and endometrium.—*E.C.H.*

DINGEMANSE, E., AND E. LAQUEUR.

The excretion of estrogenic hormone in the urine and feces of a woman during the menstrual cycle. *Nederland. tijdschr. v. geneesk.* 84: 3287. 1940.

The estrogens were assayed in the urine of three healthy women during one or more cycles. In *cases A* and *B* the excretion amounted to 5,560 and 5,670 I.U. In *case C* the excretion was 3,845 I.U. in another cycle. The lowest levels of excretion were always reached during menstruation, the highest levels during the intermenstrual phase. The lowest amount excreted per 24 hours was 20 I.U., the highest amount 750 I.U. The excretion of estrogens during one cycle has two points of culmination: one climax is in the middle of the cycle, the other on the 20th–22nd day after the beginning of the last menstruation. The "free" estrogens reach a climax of excretion coincidently with the climax of total excretion. The ratio between non-ketonic and ketonic estrogenic compounds in the urine was 1 during menstruation and 2 during the intermenstruum. A large proportion of the non-ketonic fraction of estrogens consists of estriol. Estrogens were also found in feces, the main portion of them being in the "free" state. Their quantity amounted to 60 to 70% of that excreted in the urine. The non-ketonic fraction appeared to consist mainly of estriol.—*R. Beutner.*

DINGEMANSE, E.

The appearance of comb-growth promoting substance in the urine following injection of testosterone propionate, androsterone and dehydroandrosterone. *Arch. internat. de pharmacodyn. et de thérap.* 65: 259. 1941.

After daily subcutaneous injections of 25 mg. of testosterone propionate in patients with prostatic hypertrophy, substances stimulating comb-growth were excreted in the urine in amounts equivalent to 6%, expressed as testosterone propionate, or 24%, expressed as androsterone, of the amount of testosterone administered. In male dogs, daily injections of 40 mg. of androsterone did not cause the appearance of comb-stimulating substances in urine, but in patients the daily administration of 20 mg. resulted in a notable increase in excretion of these substances. In 1 patient treated with androsterone and testosterone propionate, excretion of comb-stimulating substances was still increased 1 month after treatment. During treatment with testosterone propionate, the excretion of estrogenic substances was also increased.—*G.A.E.*

DRAPER, J. W., G. SLAUGHTER AND C. DENSLOW.

The effect of testosterone propionate on benign prostatic hypertrophy. *J. Urol.* 45: 539. 1941.

Fourteen cases of early prostatic hypertrophy without complicating factors were given a basic treatment of 25 mg. of testosterone propionate hypodermically each day for 2 weeks. The dosage was varied in individual cases and sterile salt solution was substituted at times for the active drug, as a control. There is a brief analysis of each case. The authors conclude, "We have observed no apparent improvement in the urinary status of our cases of early benign hypertrophy resulting from injection of testosterone which could not be duplicated by injections of sterile saline."—*J.C.D.*

FINKLER, R. S., AND G. M. COHN.

The oral administration of methyl testosterone in a male castrate. *J. Urol.* 45: 548. 1941.

This is a case report comparing the undesirable effects of testosterone given intramuscularly with the satisfactory results following oral administration. The authors state "Oral therapy with methyl testosterone in a male castrate proved to be adequate for the control of the following symptoms: headaches, crying spells, gain in weight, despondency and loss of libido. The external genitalia increased in size and the metabolic rate rose from −14 to +6%."—*J.C.D.*

GREENBLATT, R. B., E. MCCALL AND R. TORPIN.

Oral progestin (anhydro-hydroxy-progesterone) in the treatment of dysmenorrhea. *Am. J. Obst. & Gynec.* 42: 50. 1941.

Anhydro-hydroxy-progesterone was administered orally (in monthly doses) ranging from 20 to 240 mg., given from 2 to 22 days premenstrually) during 64 cycles of 30 patients with dysmenorrhea. Relief during treatment cycles was 'satisfactory' in 50% of these, 'partially so' in 22% and failed in 28%. Studies of endometrial responses in 17 of the 30 patients indicated that no interference with ovulation followed therapy.—*E.C.H.*

GREENBLATT, R. B., AND E. A. WILCOX.

Hormonal therapy of fibromyomas of the uterus. *South. Surgeon* 10: 339. 1941.

Six patients with small palpable uterine fibromyomata and severe hypermenorrhea with or without dysmenorrhea or lower abdominal pain were treated with androgenic substances, either 20–75 mgm. of testosterone propionate per month, administered subcutaneously in divided doses or methyl testosterone administered orally in

doses of 10 mgm. per day for 10 or 15 days during the intermenstruum. As a result of treatment with either preparation, menorrhagia was controlled, dysmenorrhea and lower abdominal pain were eliminated and libido and feeling of well-being increased. No virilizing symptoms were noted. Therapeutic results were not permanent; recurrences followed several months after cessation of therapy. However, growth of the tumors appeared to be held in abeyance. Ten patients with massive uterine fibromyomas and excessive uterine bleeding were treated by the implantation upon the thigh muscles of 25 to 145 mgm. pellets (1 in each case) of testosterone propionate. All were promptly relieved of pelvic discomfort, excessive bleeding and dysmenorrhea. The tumors appeared to diminish. Increased libido and a sense of well-being was present in each patient after pellet implantation. During an observation period of 3 to 9 months, no virilizing symptoms were noted and the implant scars remained smooth, soft and without palpable deep induration. The therapeutic results in these cases were interpreted as lending support to the view that the excessive bleeding frequently associated with fibromyomata of the uterus is not due to mechanical factors but to endocrine imbalance.—*Doris Phelps.*

HAMBLEN, E. C.

Some observations on the endocrinology of abortion. *Am. J. Obst. & Gynec.* 44: 664. 1941.

General concepts of the hormonology of abortion are considered and studies of progestin metabolism (ovarian and placental) in pregnancy and in recurrent abortion are reviewed. The detailed case records of 6 pregnant women who either had had repeated abortions or who were threatening to abort are presented for the purpose of evaluating their pregnandiol titers and the effects upon these of their various therapies. Pregnandiol titers, as a rule, tend to fall prior to abortion; this fall may be abrupt or gradual. During the course of pregnancy prior to the onset of abortion, titers may be normal or low. Patients may threaten to abort when pregnandiol titers are normal. Intensive therapy with progesterone, alone or combined with estrogens and chorionic gonadotropin, fails to elevate low pregnandiol titers and to prevent abortion under these circumstances. There is a likelihood that large doses of progesterone may precipitate abortion by depressing the metabolism of intrinsic progestin.—*E.C.H.*

HAMILTON, J. B.

Therapeutics of testicular dysfunction. *J.A.M.A.* 116: 1903. 1941.

The treatment of male hypogonadism is discussed under the following headings: anterior hypophysis-testicular relationships, castration and eunuchoidism, other testicular dysfunction states, and finally the limitations, contraindications, and dangers of therapy.—*C.P.*

HENDERSON, D. N.

The incidence of endometrial hyperplasia with uterine fibroids and external endometriosis (adenomyosis). *Am. J. Obst. & Gynec.* 41: 694. 1941.

Study is based upon uteri from 727 cases of fibromyomata, 108 of extrauterine endometriosis and 82 of intrauterine endometriosis. The incidence of the swiss cheese pattern of endometrium under these conditions was: in 6.5% of the fibromyomata cases, in 9.2% of the external endometriosis ones and in 25% of the internal endometriosis ones.—*E.C.H.*

JONES, G. E. S., AND R. W. TELINDE.

The metabolism of progesterone in the hysterectomized woman. *Am. J. Obst. & Gynec.* 41: 682. 1941.

A normal woman in the interval phase of the cycle and 3 hysterectomized women were given 40–60 mg. of progesterone daily for 3 days and pregnandiol titers established. Essentially similar pregnandiol values were found in all 4, being equivalent to a recovery of 10.9 to 15.6% of the progesterone injected. A patient hysterectomized on the 1st day of her cycle, excreted 6.1 mg. of pregnandiol during the 16th and 17th days of her cycle. One of 3 patients hysterectomized 6 mo. or more previously, judged to be in the luteal phase of their cycles by studies of cervical mucus and studied during this time for pregnandiol excreted, excreted 3.3 mg. of pregnandiol.—*E.C.H.*

LAMPTON, A. K., AND A. J. MILLER.

The influence of temperature on the internal secretory activity of transplanted ovaries in the male rat. *J. Urol.* 45: 552. 1941.

The effect of temperature on the internal secretory activity of transplanted ovaries was investigated by grafting ovaries into the ears of castrate male rats, 7 of which were kept at 33°C. and 10 at 22°C. These animals were studied for excretion of urinary androgens, histological changes in the prostate and seminal vesicles, castration changes in the pituitary gland. That transplanted ovaries, which are kept warm by a high environmental temperature, secreted less androgenic substance than do those kept cool by a low environmental temperature was shown by the diminished urinary androgens, more severe atrophy in the prostate and seminal vesicles, more negative ejaculation tests and the presence of castration cells in more of the pituitary glands of the animals of the former group.—*Authors' summary.*

LANGMAN, L., AND H. S. BURR.

An electrometric study of uterine activity. Preliminary report. *Am. J. Obst. & Gynec.* 42: 59. 1941.

The method employed consisted of connecting a vacuum tube microvoltometer to the cervix by means of wires terminating in metal clips which gripped the lips of the cervix (the ground electrode to posterior lip, the hot electrode to the anterior lip) and of recording resultant changes in voltage by means of a General Electric photoelectric recorder. A total of 56 recordings (lasting from ½ to 3 hours each) were made on 17 patients, including before and after therapy observations, the therapy embracing ergotrate intravenously, pituitrin, progesterone and estradiol benzoate. These studies indicated that records of the slowly changing standing potential between the dorsal and ventral lips of the cervix could be correlated

with phasic changes during menstruation and with the administration of various hormones and oxytoxics. The bio-electric effects following progesterone were judged indicative of a quieting action upon uterine hypermotility. These correlates indicated, on the other hand, that the uterus is responsive to pituitrin during all phases of the cycle. Likewise, the observations after injections of estradiol benzoate were interpreted as indicative of myometrial stimulation.—*E.C.H.*

LULL, C. B.

Pubertas praecox due to ovarian tumors. *Am. J. Obst. & Gynec.* 41: 445. 1941.

Two cases, one patient 9 months, the other 22 months of age, are reported and discussed. The pathology in the first case was a granulosal cell tumor and in the second a simple follicular cyst. Satisfactory clinical responses followed surgery in both cases.—*E.C.H.*

MCCULLAGH, E. P., AND R. JONES.

A note on the effect of certain androgens upon the red blood cell count and upon the glucose tolerance. *Cleveland Clin. Quart.* 8: 79. 1941.

Changes in B.M.R., pulse rate, weight and blood picture are described in a case of male hypogonadism in which androgen therapy was administered over a period of 8 years. The androgens used were androtin, testosterone propionate (5–50 mg. daily) and methyl testosterone (50–150 mg. daily). Periods of treatment were followed by increase in body weight, B.M.R. and R.B.C. count, relatively little change in pulse, and a decreased tolerance for glucose.—*E. Cutuly.*

MCCULLAGH, E. P., AND R. JONES.

Effect of certain androgens on the red blood cell count and on the glucose tolerance. *Cleveland Clin. Quart.* 8: 79. 1941.

The administration of methyltestosterone (I) to patients suffering from hypogonadism resulted in a rise in the number of red blood cells (II). Withdrawal of I resulted in a decrease of II. I also produced a decrease in tolerance to sugar (III) as suggested by prolongation of the sugar-tolerance curve in 7 cases treated with I. The authors attribute this to a decrease in deposition of III in the liver. —*I. Arthur Mirsky.*

MAIN, R. J.

The assay of urinary gonadotropin in cases of testicular tumor. *Virginia M. Monthly* 68: 381. 1941.

A clinical laboratory technic for the assay of gonadotropin is described using alcohol precipitation, and uterine weights and vaginal smears of rats as the end point.—*R. J. Main.*

MICALE, G.

Retention of corpus luteum after removal of gravid uterus. *Boll. Soc. ital. biol. sper.* 15: 381. 1940.

Daily administration of ascorbic acid (50 mg.) or gonadotropic hormone (50 R.U.) had no effect; folliculin (35μg.) or vitamin E led to retention of corpora lutea, resembling those of pregnancy.—*B.C.P.A.*

MISHELL, D. R.

A clinical study of progesterone therapy by pellet implantation. *Am. J. Obst. & Gynec.* 41: 687. 1941.

Results of the implantation of progesterone tablets weighing 45 to 60 mg. are described. Four patients with histories of recurrent or threatened abortion were treated: one delivered at term, others now 8, 6 and 3 months' gravid and progressing normally. Six dysmenorrheic women were treated with satisfactory results over 3 to 6 months being obtained in 4. Four menorrhagic women were treated; satisfactory effects on bleeding and on endometrial responses (estrogenic→progestational) were obtained in 2.—*E.C.H.*

MISHELL, D. R.

A clinical study of estrogenic therapy with pellet implantation. *Am. J. Obst. & Gynec.* 41: 1009. 1941.

The report is based upon studies of the effects of the implantation of a single pellet (45 to 65 mg. in weight) of crystalline estrogens in 28 patients with menopause or amenorrhea. Brief case protocols are given. The author concludes that this form of therapy is safe, effective and economical.—*E.C.H.*

MON. R.

Gonadotropic hormones in the amniotic fluid. *Rev. sud-am. de endocrinol.* 24: 161. 1941.

The content of gonadotropic hormone was investigated in the amniotic fluid of 20 cases of pregnancy. Two times the concentration was 750 U., 16 times 1,000 U. and 2 times 1,200 U.—*A.E.M.*

NATHANSON, I. T., LOIS E. TOWNE AND J. C. AUB.

Normal excretion of sex hormones in childhood. *Endocrinology* 28: 851. 1941.

From 3 to 7 years of age, both boys and girls excrete a small and constant amount of estrogens and 17-ketosteroids in the urine, with little difference between the sexes. From 8 to 11 years of age there is an increased excretion of these sex hormones; 17-ketosteroids increase more rapidly in boys, estrogen in girls. About 1½ years before the menarche, estrogen excretion becomes cyclic in girls; and the intensity of these cycles gradually increases. The appearance of estrogen cycles precedes the dramatic sexual development of girls before the menarche. No cycles are obvious in the excretions of boys. There is no cycle in 17-ketosteroid excretion in either sex. Boys have a higher excretion, especially after 11 years of age when secondary sex characteristics begin to appear. At 11 years of age the follicle stimulating hormone of the anterior pituitary gland in the urine of girls was first detected, but in boys it appeared somewhere between the 12th and 13th year. This late appearance may be due to the inefficiency of the method. It appears clear, therefore, that the menarche in girls and the sexual maturity of boys are the culmination of an endocrine development which starts about 5 years before puberty. This is gradual until ap-

proximately 1½ years preceding maturity, when an additional mechanism appears which leads to more rapid differentiation of sex characteristics and eventually complete metamorphosis.—*Authors' summary.*

NATHANSON, I. T., R. B. MILLER, LOIS E. TOWNE AND J. C. AUB.

The close correlation of androgen and creatinine excretion in normal children. *Endocrinology* 28: 866. 1941.

In growing children, both girls and boys, there is a close correlation between the excretion of the 17-ketosteroids and of creatinine. The correlation of the 2 substances is so close it seems highly likely there is a fundamental relationship. The most likely explanation appears to be that androgens have an influence on the muscle mass of the individual so that an increase of androgen formation would result in an increased muscle mass, and therefore the creatinine excretion rate.—*Authors' abstract.*

NEUSTAEDTER, T.

The effect of oral administration of alpha estradiol and pregneninolone upon the human castrate uterus. *Am. J. Obst. & Gynec.* 42: 86. 1941.

Six female castrates were treated with α-estradiol and anhydro-hydroxy-progesterone (total oral doses of 120 mg. and 1,200 mg., respectively). Progestational endometria followed therapy in all cases.—*E.C.H.*

PALMER, A.

Clinical experiments with diethylstilbestrol. I. Estrogen withdrawal bleeding in primary and postmenopausal amenorrheic women. *Am. J. Obst. & Gynec.* 41: 861. 1941.

Cyclic episodes of uterine bleeding were produced by cyclic diethylstilbestrol therapy in 4 patients with primary amenorrhea and in 4 patients with postmenopausal amenorrhea. Forty-two mg. of diethylstilbestrol were found to be adequate, when given over a 14-day interval, to produce sufficient endometrial proliferation for uterine bleeding. Seventy mg., given over 14 days, produced slight hyperplasia of the endometrium. There was a consistency of the latent interval which preceded withdrawal bleeding which was irrespective of dosage or manner of administration of the estrogen.—*E.C.H.*

PALMER, A.

Clinical experiments with diethylstilbestrol. II. The treatment of uterine bleeding. *Am. J. Obst. & Gynec.* 41: 1018. 1941.

Thirty-one patients with excessive functional bleeding, ages ranging from 12 to 55 years, were treated according to a cyclical regime with diethylstilbestrol. For young women the schedule was: Therapy began on the 3rd day of bleeding. One mg. of diethylstilbestrol was given daily for 7 days, then 5 mg. daily for 7 days and subsequently 0.3 mg. daily for 10 days or until bleeding began. For older women (with menopausal bleeding) 5 to 15 mg. of stilbestrol a day was given until bleeding ceased and a maintenance dose of 1 to 2 mg. a day was continued for 3 weeks or until bleeding recurred. Cessation of abnormal bleeding was the end-point of therapy. Cycles of therapy required for regulation of bleeding varied in number from 1 to 5. No consistency occurred in length of the latent period between cessation of therapy and onset of bleeding. Excessive bleeding was controlled in all patients. The author cautions this effect may be only temporary at times but recurring hemorrhages respond to additional therapy.—*E.C.H.*

PRINS, C. W.

Hormonal treatment of retentio testes. *Nederl. tijdschr. v. geneesk.* 85: 758. 1941.

Good results after treatment with an anterior-pituitary-like preparation (from pregnancy urine).—*R. Beutner.*

REPORT OF THE COUNCIL ON PHARMACY AND CHEMISTRY. *J.A.M.A.* 116: 1054. 1941.

Pregneninolone, a derivative of testosterone, induces progesterone-like changes in the uterus, but unlike progesterone this product is effective by mouth. The report concludes that since the clinical data are inconclusive, pregneninolone is not acceptable, at present, for inclusion in the N.N.R.—*C.P.*

REPORT OF THE COUNCIL ON PHARMACY AND CHEMISTRY. *J.A.M.A.* 116: 1523. 1941.

The therapeutic uses of progesterone are reviewed and a critical discussion of its use in habitual abortion, dysmenorrhea, and functional bleeding is given. The report concludes that the clinical evidence does not, at present, warrant the acceptance of progesterone for inclusion in the N.N.R.—*C.P.*

REYNOLDS, S. R. M., S. KAMINESTER, F. I. FOSTER AND S. SCHLOSS.

Psychogenic and somatogenic factors in the flushes of the surgical menopause. *Am. J. Obst. & Gynec.* 41: 1022. 1941.

Eighteen patients were studied (13 with artificial menopause, 4 in natural menopause and 1 cyclic). Seven responded promptly and satisfactorily to estrogenic therapy as regards their flushes. Eleven (10 in artificial menopause and 1 who still menstruated) secured no relief from estrogens or phenobarbital. These patients either responded to correction of neuroses or medical problems or their complicating factors were of such magnitude as to prevent adequate adjustments. The authors, accordingly, regard the psychogenic factor as a contributing, and not merely coincidental, element in the production of flushes in artificial menopause.—*E.C.H.*

ROTHERMICH, N. O., BEATRICE POSTLE AND L. M. FOLZ.

Altered concept of therapy of involutional melancholia with estrogen and androgen. *Arch. Neurol. & Psychiat.* 45: 752. 1941.

In 24 cases of classic involutional melancholia and 10 of atypical involutional psychosis sex-hormone therapy was administered in sufficient dosage to bring about objective evidence of effect. Of the first group 5 showed some degree of mental improvement but little more than would

have been expected without hormone treatment. In the atypical group 7 of the 10 showed improvement grading up to apparent cure. Of the 12 showing improvement 7 had had testosterone and 5 estrone. It is concluded that in true involutional melancholia endocrine therapy is of doubtful value but in other depressions of the climacteric remarkable improvement may ensue. Androgens and estrogens are of practically equal value.—*R.G.H.*

Rubenstein, B. B., and D. R. L. Duncan.

A technic for assay of estrogen by evaluation of human vaginal smears and comparison with urinary estrogen assay on the mouse uterus. *Endocrinology* 28: 911. 1941.

A technic of evaluation of human vaginal smears in terms of estrogen on a scale 0–4 is presented. The assay by human smears roughly parallels the assay of urinary estrogen excretion using the mouse uterus weight response. The human vaginal smears taken with proper precaution may be used as a rough assay of the patient's estrogen.—*Authors' summary.*

Rubinstein, H. S., and A. A. Kurland.

Effect of small doses of testosterone propionate on testis and accessory sex organs. *J. Urol.* 45: 780. 1941.

Seventy-two male albino experimental rats and 24 litter mate controls were used. Testosterone propionate was given subcutaneously in 2.5, 5, or 10γ doses starting when the rats were 22 days old. Treatment ran daily for 10 or 20 days. The 2.5γ dosage had no effect. In the 10 day series the 5 and 10γ dosage led to a "probably significant" increase in weight of the prostate and seminal vesicles. These organs were, however, unaffected by the above dosages in the 20 day series though in this case the testis was "suggestively depressed." The adrenals were unaltered by any of these treatments.—*J.C.D.*

Salmon, U. J., S. H. Geist, J. A. Gaines and R. I. Walter.

The treatment of abnormal uterine bleeding with androgens. *Am. J. Obst. & Gynec.* 41: 991. 1941.

A comprehensive and detailed account of 3 year experience with the use of testosterone propionate in the treatment of 61 patients with abnormal uterine bleeding is given. Included in this report are: recommendations as to optimal dosage, a discussion of safeguards against masculinizing phenomena and a preliminary report on the value of the implantation of methyl testosterone, ethinyl testosterone and testosterone. The 61 patients treated were distributed as follows: 45 had functional bleeding, 15 had menometrorrhagia associated with uterine fibroids and 1 had adenomyomatosis. Good primary therapeutic results were secured in 97.7% of the patients with functional bleeding. Apparent cures occurred in 66.6% of these patients. Primary results were good in 87% of the patients with fibroids, but excessive bleeding recurred in 60% after discontinuation of therapy. Unsatisfactory results were obtained with implanted pellets of testosterone and testosterone propionate. A theory regarding the modus operandi of androgenic therapy in functional bleeding and one regarding their physiologic role in the female are presented.—*E.C.H.*

Schellekens, W. M. J.

Synthetic estrogens (estromenin) in gynecology. *Nederl. tijdschr. v. geneesk.* 84: 940. 1940.

Estromen or "cyren" which is 4.4-dioxy-a-b-diethylstilbene is applied in an ointment, or injected in oil in hypomenorrhea, dysmenorrhea, pruritus vulvae and other gynecologic disorders.—*R. Beutner.*

Segal, H. I., A. Steinberg, F. R. Shechter, N. H. Colton and N. Pastor.

An attempt at endocrine correlation and therapy in 125 cases of menstrual disorders. *Am. J. Obst. & Gynec.* 41: 979. 1941.

A statistical study of the incidence of menstrual disorders and the diagnosed endocrinopathy of 125 patients is presented. The basis for diagnostic data included history, physical examination, routine laboratory studies, 5-hour glucose tolerance test, blood calcium and phosphorous, B.M.R. studies, blood cholesterol and Volhard fluid-retention test, where indicated. A quantitative estimation of urinary gonadotropin (extraction method of Katzman and Doisy; assay method of Collip) and one of urinary estrogens (extraction method of Gallagher, Koch and Dorfman) were done on most patients. Dysmenorrhea, oligomenorrhea, hypomenorrhea and premenstrual tension occurred most frequently in hypopituitary patients. Menorrhagia predominated in hypothyroidism, while hypermenorrhea, polymenorrhea and metrorrhagia occurred most often in hypopituitarism. Therapy with endocrine agents chosen on the basis of the endocrinopathy diagnosed and given according to described therapeutic schedules was reported to have resulted in marked improvement in over 50% of cases.—*E.C.H.*

Sevringhaus, E. L.

Treatment of the menopause. *J.A.M.A.* 116: 1197. 1941.

Under the therapeutics of the menopause the following factors are stressed: 1. The need for estrogen standardization on a dry-weight basis. 2. The oral administration of estrogens is effective, as shown by the relief of symptoms and restoration of vaginal epithelium. 3. If prices can be adjusted, the clinician can then obtain comparable results with whichever preparation he prefers.—*C.P.*

Smith, O. W., and G. V. S. Smith.

Increased estrogenic potency of human urine after zinc-hydrochloric acid hydrolysis. *Endocrinology* 28: 740. 1941.

Experiments on 3 estrogens known to be present in human urine reveal that Zn-HCl hydrolysis does not affect the potency of crystalline estradiol or estriol, but in the proper medium, completely converts any estrone that escapes destruction into some product of greater activity. Estradiol is produced from Zn-HCl-hydrolyzed estrone, and may be the only end product. Experiments on Zn-HCl-hydrolyzed urine reveal that estrone conversion cannot be the only source of the increased potency observed, since the end product of Zn-HCl-hydrolyzed urine differs both qualitatively and quantitatively from the end

product of Zn-HCl-hydrolyzed estrone. Determination of the possible sources, other than estrone conversion, of the difference between total estrogen after Zn-HCl hydrolysis and total estrogen after HCl hydrolysis shows that a large part of the highest proportional increases is derived from nonestrogenic urinary constituents which are rendered estrogenic by Zn-HCl hydrolysis. The highest ratios of total estrogen after Zn-HCl hydrolysis to total estrogen after HCl hydrolysis are found in specimens in which the partition of the urinary estrogens reflects estrogen destruction. These high ratios may be due to rehydrogenation of oxidized estrogen breakdown products. Zn-HCl hydrolysis is not suitable for the study of urinary estrogens as such, and if used extensively, would lead to entirely misleading conclusions concerning estrogen metabolism. The ratio of total estrogen Zn-HCl hydrolysis to total estrogen after simple HCl hydrolysis provides a relative index of estrogen destruction in the body.—*F. Saunders.*

Spalding, H. C., R. J. Main and J. L. Patterson.

Dysmenorrhea-like episodes in a patient with congenital absence of the uterus. *Virginia M. Monthly* 68: 105. 1941.

Daily assays of concentrated urine from a female with congenital absence of the uterus, failed to show any gonadotropin excretion. The authors suggest that the absence of the uterus may be a factor.—*R. J. Main.*

Stewart, H. L., Jr., and J. P. Pratt.

Inhibition of lactation. *Am. J. Obst. & Gynec.* 41: 555. 1941.

A previous study of normal lactation among 900 consecutive nursing mothers had indicated that the degree of early breast engorgement did not indicate the amount of milk subsequently produced. To determine whether inhibition of breast engorgement was synonymous with the inhibition of lactation, nursing mothers were given stilbestrol, estrone or testosterone either during the first 2 or 3 days of the puerperium or during the 5th and 6th days after delivery and the effect on engorgement and milk secretion determined. Inhibition of breast engorgement was not synonymous with inhibition of lactation. The former may be prevented with suitable doses of stilbestrol, estrone or testosterone. Lactation, however, may be diminished temporarily at times by stilbestrol, whereas the effects of 250,000 I.U. of estrone and 125 mg. of testosterone on lactation are negligible.—*E.C.H.*

Stone, E. T. R.

The use of testosterone propionate in the management of pelvic inflammatory disease. *Am. J. Obst. & Gynec.* 42: 114. 1941.

Stone reports an attempt to treat pelvic infection by suppressing menstruation with testosterone propionate. Case reports of 6 patients are given. Testosterone propionate was given in 25 to 50 mg. doses, 2 to 3 times weekly. Amount necessary to suppress menses varied from 350 to 650 mg. per month; successful results in this regard were obtained in all cases. No flare-ups occurred during period of treatment. In 5 of the 6 patients, the pelvic inflammatory masses decreased and in one these disappeared completely.—*E.C.H.*

Strassmann, E. O.

The theca cone and its tropism toward the ovarian surface, a typical feature of growing human and mammalian follicles. *Am. J. Obst. & Gynec.* 41: 363. 1941.

An 18 year study of over 18,000 serial sections of ovaries of Primates (man), Carnivora (dog, cat), Rodentia (rabbit) and Ungulata (horse, cow, swine) is reported. The findings are judged to warrant acceptance of the theca interna cone as an integral part of the mechanism of ovulation. It apparently functions as a pathmaker for the ascent of growing follicles to the ovarian surface. It has been found present in all mammalian species examined. It is associated only with growing follicles, disappearing as soon as degeneration occurs. Accordingly, it is suggested that its appearance can be used as a test for ovarian response to gonadotropic stimuli.—*E.C.H.*

Tholen, M. H. G. A., and Wr. S. Koops.

Experience with hormone implantation. *Nederl. tijdschr. v. geneesk.* 84: 2440. 1940.

Favorable results in menopausal conditions occurred with implantations of estrogenic hormones.—*R. Beutner.*

Turner, S. J., and S. J. Zakon.

Herpes gestationis. *Am. J. Obst. & Gynec.* 41: 525. 1941.

Estrogenic and corpus luteum therapy failed to modify the course of a reported case of herpes gestationis.—*E.C.H.*

Vogt, W. H., and D. L. Sexton.

Treatment of menstrual disorders with pregnant mare's serum. *Am. J. Obst. & Gynec.* 42: 81. 1941.

Seventeen patients with amenorrhea, oligomenorrhea, hypomenorrhea and menorrhagia were treated with equine gonadotropin (200 I.U. daily for 15 days, followed by rest period and a repetition of therapy if no response: patients with amenorrhea and hypomenorrhea were primed with estrogens, 16,000 U. being the usual preliminary dose. One of the 2 patients with amenorrhea had resumption of cyclic bleeding. All 4 patients with menorrhagia were benefited, 1 becoming pregnant. Of the 11 patients with oligo- and hypomenorrhea, 8 experienced no clinical results. Endometrial studies before and after therapy in 11 patients indicated no induction of progestational responses.—*E.C.H.*

Wang, Y., and Shueh-P'ing T.

The metabolism of sterols. I. Excretion of pregnanediol glucuronide in the urine of Chinese pregnant women. *Chinese J. Physiol.* 16: 121. 1941.

Venning's gravimetric method for extraction of Na pregnanediol glucuronide (I) from urine was modified, since n-BuOH was not available; iso-BuOH was used instead. The extracting power of iso-BuOH is only 64% as great as that of n-BuOH. The daily excretion of I of

Chinese women does not differ from that of Americans. In early twin pregnancy (3 mos.) 150% more I was excreted (30 mg.) than the average in single pregnancy (12 mg.). In the 4th month it reached a maximum (81 mg.) and then decreased.—*T. Laanes.*

WIJSENBEEK, I. A., AND W. P. PLATE.

A case of arrhenoblastoma of the ovary with hormone investigation. *Nederl. tijdschr. v. geneesk.* 84: 1022. 1940.

Description of a case of arrhenoblastoma in the wall of a cyst, containing 3 l. of fluid in which 170γ of androsterone and 100γ of testosterone with only traces of estrogenic hormones. The tumor contained 6 I.U. of substances stimulating comb growth and 50 U. of estrogenic material.—*R. Beutner.*

## PANCREAS

DRY, T. J., AND E. A. HINES.

The role of diabetes in the development of degenerative vascular disease: with special reference to the incidence of retinitis and peripheral neuritis. *Ann. Int. Med.* 14: 1893. 1941.

The authors postulate that a biologic background exists for the development of advanced arteriosclerosis in the presence of diabetes mellitus, i.e., an inherent weakness or abiotrophy exists which affects both the insulin-producing tissues and the vascular system, which requires in each instance an additional stimulus to bring about pathologic changes in the structure of the insulin-producing tissues and the vascular system. In the case of the former, an infectious illness, overfeeding, or obesity, and in the case of the latter, hypertension, obesity or hyperlipemia, may serve as adequate stimuli for the initiation of the lesion, or of the progression of the lesion, once it has been initiated. This phenomenon is analogous to the variability in the vulnerability of different animals to arteriosclerosis under experimental conditions, for example, during the feeding of cholesterol. On the basis of the frequent association of arteriosclerosis obliterans, retinitis, and peripheral neuritis among diabetic patients and on the basis of certain anatomic observations made in the presence of retinitis and neuritis, it is postulated that a common mechanism exists for the production of these 3 entities; namely, involvement of the nutrient vessels concerned in each instance; in retinitis, the retinal arterioles; in neuritis, the vasa nervorum; in intimal arteriosclerosis, the vasa vasorum.—*Authors' abstract.*

EDITORIAL.

Fat Metabolism in Diabetes Mellitus. *J.A.M.A.* 116: 2403. 1941.

A summary is given of the revised concept of the role of ketone bodies in diabetes. The old aphorism of ketone bodies burning in the flame of the carbohydrate is superseded by the statement that when carbohydrate will not burn, more fat must be incompletely burned to fulfil energy requirements.—*C.P.*

EDITORIAL.

Necrobiosis lipoidica diabeticorum. *J.A.M.A.* 116: 953. 1941.

This editorial calls attention to the skin lesions consisting of hard flat papules bluish violet at the border and yellow in the center which are seen occasionally in the legs of diabetics. While due to an infiltration with lipids, the lesion is chronic and is resistant to insulin, low fat diet, and to roentgen or ultraviolet irradiation.—*C.P.*

HURWITZ, DAVID.

Pregnancy accidents in diabetes. *J.A.M.A.* 116: 645. 1941.

Hurwitz criticizes the paper by White on the following grounds. 1. Inadequate controls—since pregnancy accidents also occur in patients with a normal hormonal balance and imbalance tend to spontaneous correction. 2. The Boston Lying-in Hospital has obtained comparable results to those of White's without any therapy. He suggests that the enthusiastic sponsorship of hormone therapy be postponed to await more convincing data. In reply White states that her series was adequately controlled but the nature of the control not elaborated for purposes of brevity. The causes of fetal death are also clarified. Joslin summarizes in a letter commending White's findings.—*C.P.*

KAUFMAN, R. E.

Influence of thiamine on blood sugar levels in diabetic patients. *Arch. Int. Med.* 66: 1079. 1940.

Thiamine in daily dosage of 1,000 I.U. in addition to the amount in the food was given orally for periods of 5 to 8 weeks to 10 well controlled diabetic patients. Four patients showed an elevation of the average level of blood sugar while taking thiamine; 4 showed no appreciable change, and 2 showed a lowering. Statistical analysis indicates that these variations are due to chance and not to any specific factor, such as the therapeutic agent under investigation. Since no improvement in the average level of hyperglycemia was noted during the administration of thiamine, it is concluded that use of this vitamin is not indicated as a routine measure for diabetic patients.—*I.B.*

LANDBAEK, K., AND G. MAGNUSSEN.

The carbohydrate metabolism in insulin shock therapy. *Acta med. Scandinav.* 105: 447. 1940.

Twenty patients (11 women, 9 men) on insulin shock therapy were placed on standard diets containing either 50 or 500 gm. of carbohydrate daily and at suitable intervals changed to the other diet. In addition the patients received 200 gms. of carbohydrate to interrupt the coma if on the high carbohydrate diet and 50 to 150 gms. if on the low carbohydrate diet. Glucose and insulin tolerance tests were carried out on each patient during the study. The blood sugar values on the low carbohydrate diet rose higher on the glucose tolerance test and remained higher on the insulin tolerance tests. The amount of insulin required to produce coma was decreased when changing from a high to a low carbohydrate diet and was increased on the reverse change. The relationship between diet and

insulin or glucose tolerance remained fundamentally unchanged under insulin shock therapy.—*J.M.L.*

LAWRENCE, R. D., AND KATE MADDERS.

Human diabetes treated with oestrogens. *Lancet* 240: 601. 1941.

Lawrence and Madders have given 5 women diabetics of menopausal age 1 mg. of stilbestrol 4 times daily for 8 weeks with no apparent effect on the diabetic condition. War conditions have prevented completing tests on a large number of cases, but these few results are given because they are clear cut and agree with Young's experiments on diabetic dogs.—*J. B. Paton.*

MCDANIEL, L. T., H. H. MARKS AND E. P. JOSLIN.

Diabetes mellitus and syphilis. A study of two hundred and fifty-eight cases. *Arch. Int. Med.* 66: 1011. 1940.

The authors present a study of 258 cases of diabetes with syphilis from a total of 15,095 cases of diabetes. The chief factors in the causation of diabetes (positive heredity history of diabetes, the state of being overweight and the age at onset of diabetes) have been shown to be the same for diabetic patients with syphilis as for diabetic patients without syphilis. If "syphilitic diabetes" occurs, theoretically it would most likely be a late manifestation of syphilis occurring in older persons, except in patients with congenital syphilis, in whom diabetes is uncommon. Part of the evidence against the relationship of the diseases is the marked difference between the sexes in the duration of syphilis before the onset of diabetes. For evaluation of results of antisyphilitic therapy, a diabetic patient with syphilis must be regulated on a constant diabetic regimen. A diabetic patient with syphilis may be given antisyphilitic treatment with the same considerations given to any patient concerning the plan of treatment. To be certain that antisyphilitic treatment has improved or cured diabetes, a case must be followed for years and the condition checked with dextrose tolerance tests. In this series there was not a single instance of cure of diabetes brought about by optimum antisyphilitic treatment. On the average, a patient with syphilis and diabetes does not appear to have any type of diabetes different from that of the usual patient of the same age. The authors have not been able to recognize the characteristics of such a clinical entity as "syphilitic diabetes."—*I.B.*

MARTIN, HELEN E., AND P. O. GREELEY.

Time-activity curves of protamine zinc insulin. Clinical application and significance of such curves in the treatment of patients with severe diabetes. *Arch. Int. Med.* 67: 194. 1941.

The authors discuss the importance of measuring insulin action on a time-activity basis. Time-activity curves of large doses of protamine zinc insulin in the depancreatized dog and in the patient with severe diabetes are presented. These curves show graphically the slow onset of activity, with delayed peak of activity, the long duration of action, and the relatively small amount of carbohydrate required per hour, as compared with the large total amount of carbohydrate required. The clinical application of such curves is discussed, with particular reference to the excellent control of the basal insulin requirement of certain patients with severe diabetes by use of protamine zinc insulin in amounts under 40 U., and the necessity of using more quickly acting insulins to cover the dietary load in patients with severe diabetes if postprandial hyperglycemia is to be avoided.—*I.B.*

PORTER, R. D.

Diabetes. VII. The management of pregnancy in diabetes. *Pennsylvania M. J.* 44: 148. 1940.

This is the seventh and final article of a series on diabetes published under the sponsorship of the Commission on Diabetes of the Medical Society of the State of Pennsylvania. The author's conclusions are as follows: Closest cooperation of the obstetrician and the diabetic specialist is necessary in the proper management of diabetes in pregnancy. Acidosis, even in its mildest forms, must be prevented. Acidosis, endocrine imbalance, development of fetal monstrosities, and overgrowth of the fetus cause the fetal mortality rate to be about 40% at the present time. Caesarean section must be considered in more cases than in the normal management of labor. The production of insulin by the fetus complicates the management of the diabetes during pregnancy and the management of the newborn infant. Mycotic vulvovaginitis and habitual abortion should indicate diabetic studies. Diabetic mothers seldom have adequate breast milk.—*I.B.*

POTTER, EDITH L., H. P. G. SECKEL AND W. A. STRYKER.

Hypertrophy and hyperplasia of the islets of Langerhans of the fetus and of the newborn infant. *Arch. Path.* 31: 467. 1941.

Hyperplasia of the islands of Langerhans in the pancreas at birth shows no constant relationship to maternal diabetes mellitus. Twenty-four cases have been reported in the literature and 2 have been observed by the authors in which hyperplasia and hypertrophy of the islands of Langerhans were present in the pancreas at birth in the presence of maternal diabetes. Many cases have been observed, however, in which there was no increase in islet tissue, and the amount of increase is not directly proportionate to the severity or lack of control of the disease. Five cases were found in the literature and 11 have been observed by the authors in which islet hyperplasia and hypertrophy was present in the fetal pancreas in the absence of clinical evidence of deranged sugar metabolism in the mother. Six of these infants exhibited erythroblastosis. The conclusion is reached that neither from the state of the sugar metabolism in the mother nor from clinical evidence demonstrable in the infant after birth can the appearance of the islands of Langerhans in the infantile pancreas be predicted.—*Authors' abstract.*

RERISSÉ, A.

The parotid, a gland with hypoglucemic action. *Rev. sud-am. de endocrinol.* 24: 165. 1941.

It is claimed that the parotid has an action similar to that of the pancreas. A diabetic in acidosis showed a tumor of the parotid. Insulin treatment caused not only subsidence of the acidosis but also disappearance of the tumor.—*A.E.M.*

ULRICH, H.

Clinical experiments with mixtures of standard and protamine zinc insulins. *Ann. Int. Med.* 14: 1166. 1941.

One of the disadvantages of using protamine zinc insulin in the treatment of diabetes is its frequently observed inability to prevent post-prandial hyperglycemia. Extracts were made with various mixtures of protamine zinc and standard insulins to determine whether such mixtures would combine the advantages of the rapid action of standard insulin with the prolonged action of protamine zinc insulin. A mixture of 3 parts standard insulin with 2 parts protamine zinc insulin gave the most promising results, which compared favorably with those obtained by giving separate injections of the 2 insulins. Furthermore, predictability of results was as good with the mixtures as with separate injections. The mixtures appear to possess a reasonable degree of stability. Their use should prove helpful in cases of diabetes when protamine zinc insulin alone fails to prevent elevation of the blood sugar level after meals.—*Author's abstract.*

ZONDEK, H., AND GERDA WOLFSOHN.

The secretion of the fetal islands of Langerhans. Blood-sugar analysis in the newborn. *Acta med. Scandinav.* 106: 468. 1941.

Blood was obtained either within 5–15 min. after cutting of the umbilicus or 1–17 hours later, and in a few instances before the cord was cut. Generally, the blood obtained following severance of the cord had 30–60 mg.% sugar, though 2 bloods were free from sugar. During the first few hours of life the blood sugar is subject to very wide fluctuations, even up to 300 mg.%. The rise in blood sugar bears an inverse ratio to the blood sugar level at the earlier phase. In about 5 to 7 days the blood sugar level becomes adjusted at 60–80 mg.%. Where the blood was obtained from infants before the umbilical cord was cut, the blood sugar was the same as of the mother's blood so long as there was pulsation in the cord, otherwise the blood sugar was similar to that after the cord was cut. The islands of Langerhans, which function in the fetus to store up glycogen, have such high activity as to bring about a very sudden drop in the blood sugar of the infant just as soon as its circulation becomes independent of the mother's.—*S. Morgulis.*

## PARATHYROIDS

EMERSON, K., F. B. WALSH AND J. E. HOWARD.

Idiopathic hypoparathyroidism; a report of two cases. *Ann. Int. Med.* 14: 1256. 1941.

Two cases of hypoparathyroidism of unknown etiology are reported. In one, a young boy, the disease was probably of congenital origin. There were conspicuous ectodermal defects in the hair, nails and teeth. In the 2nd case, a single woman of 56, tetanic manifestations first occurred the day following exposure to ammonia fumes. The bones of the juvenile patient showed bones of much greater density than normal, a condition which the authors believe to be characteristic of juvenile hypoparathyroidism. The elderly patient showed greatly decreased bone density, and it was thought that she suffered from so-called postmenopausal osteoporosis in addition to hypoparathyroidism. Lenticular opacities were present in the juvenile patient to only a very slight degree, whereas the elderly patient developed cataracts with extreme rapidity while under observation. In both patients the sensitivity to parathormone was tested and found normal, showing the disease to be a deficiency of parathormone rather than an increased resistance to it.—*Authors' abstract.*

GREENE, J. A., AND L. W. SWANSON.

Psychosis in hypoparathyroidism: with report of five cases. *Ann. Int.* Med. 14: 1233. 1941.

Psychosis as a complication of parathyroid tetany has been generally regarded as extremely rare. The occurrence of this complication in 5 of 18 cases of parathyroid deficiency suggests that it is not so rare. These 5 cases are reported. The psychosis is usually of a toxic delirium type, occurring during the first few months and it may be the only manifestation of parathyroid deficiency. The response to adequate treatment is usually slower than are the other manifestations and 3 to 4 weeks or several months may elapse after adequate control of the tetany before the psychosis subsides. The prognosis is good and it is not likely to recur although the parathyroid tetany may relapse.—*Authors' abstract.*

JELKE, H.

Concerning hyperparathyroidism with report of operated case with severe kidney changes. *Acta med. Scandinav. Supplement* 114. 1940.

After an extensive review of some 200 cases of osteitis fibrosa cystica described in the literature and a dissertation on its differential diagnosis, the author gives details of the case of a 58 year old ♀. The blood Ca was 19.0 mg. % before operation and fell to 6.5 mg.% after operation, which consisted in the removal of a large multiple adenoma. The kidneys showed marked calculi formation and the bones extensive decalcification with a spontaneous fracture of the right radius and left tibia. The N.P.N. was 71 mg.%. After operation the N.P.N. rose to 171 mg.% and then gradually fell to practically normal values after a month. Symptoms of tetany appeared and were controlled by Ca gluconate and vitamin D. The bones again became calcified so that the X-ray pictures at the end of 2 years were normal.—*J. M. L.*

SCHWARTZ, H. A., J. K. CURTIS AND J. V. LITCHTENSTEIN.

Hypoparathyroidism in pregnancy treated with dihydrotachysterol. *Am. J. Obst. & Gynec.* 41: 697. 1941.

A case of hypoparathyroidism following subtotal thyroidectomy is reported in which the patient's Ca metabolism continued to be regulated satisfactorily during an intercurrent pregnancy by the use of dihydrotachysterol, Ca and viosterol.—*E. C. H.*

## PINEAL

MARTIN, J.

Experimental and clinical observations on the syndrome of pineal gland destruction. *Ann. Surg.* 113: 1078. 1941.

Observations were made on the effects of extirpation of the pineal gland in immature animals, including 57 rats, 125 cats, 10 dogs and 5 monkeys. The pineal was removed at 18 days of age in rats, at 5 weeks in dogs, at 6 weeks in cats, and at 2½ months in monkeys. Removal was accomplished by means of the Horsley-Clarke stereotaxic instrument in the case of cats; in the other species the gland was removed manually by "open" operation. Observations were made on body weight, length, behavior and reproductive characteristics, and roentgenograms and photographs were secured at regular intervals. Tissue removed at autopsy was subjected to histologic study. Data were compared with similar data obtained from littermate controls of similar sex. Pinealectomized male cats matured, both sexually and in somatic development, about 5 months earlier than did their controls. Pinealectomized female cats showed no difference from their controls in somatic development, but the first estrus appeared late, litters were small and frequently dropped before term or born dead; the second generation cats were reared with great difficulty. In dogs, likewise, early somatic and sexual maturity in males and a delay in the first appearance of estrus in females was noted. The results in rats were inconclusive, although there appeared to be some hastening of maturity as a result of pinealectomy in this species also. The observations in monkeys were not described. No degeneration was found in the fiber tracts leading from the region of the pineal gland and no significant histologic changes were observed in the endocrine organs of the pinealectomized animals. The experimental results together with the clinical observation of a tendency to somatic and sexual precocity in prepuberal boys with pineal tumors and of amenorrhea in postpuberal girls of otherwise normal development, led to the conclusion that the pineal gland may function as an endocrine organ, related to the processes of sexual and somatic maturation in mammals.—*Doris Phelps.*

## THYMUS

Bomskov, C., and L. Sladović.

The thymus hormone and its biological demonstration. *Pflüger's Arch. f.d. ges. Physiol.* 243: 611. 1940.

The lipoidal fraction of thymus extract, which has been discarded by previous workers, exerts an action which the authors atrribute to the hypothetical thymus hormone. The hormone causes a disappearance of the glycogen from the livers of rats and guinea pigs. The thymus is believed to stimulate growth by this action in mobilizing carbohydrate. A second hormone elaborated by the hypophysis (the thymotropic hormone) is assumed by the authors to regulate the activity of the thymus.—*A. G.*

Bomskov, C., and K. H. Kreft.

Thymic lymphocytosis. *Pflüger's Arch. f.d. ges. Physiol.* 243: 623. 1940.

The thymus extract prepared by the authors caused lymphocytosis (92%) when injected into adult rats. The relative lymphocytosis normally observed in the young rat is considered to be a reflection of thymic activity. Lymphocytosis (36%) was also observed in man following the injection of the extract.—*A. G.*

Leriche, R., and A. Jung.

Thymusectomy for general asthenia with retardation of growth. *Presse méd.* 48: 681. 1940.

A girl whose case history had been followed from early childhood was always weak and of poor health, although not actually sick. At 16 she had the appearance of being 11 or 12 years of age. She was mentally depressed and dull, complained of feeling cold and had a dry skin. During the following year she developed an increased nervousness with frequent headaches. The weight at 17 years was 40 kg. A persistent thymus was suspected and thymectomy performed, followed by prompt improvement in every respect. The feeling of lassitude disappeared, she put on weight and grew in the following year 1.5 cm. Mentally she became alert and happier. The improvement persisted after one year.—*A. E. M.*

## HYPOPHYSIS

Adelman, M. H., and B. B. Lennon.

Pituitrin shock. *Am. J. Obst. & Gynec.* 41: 652. 1941.

Pituitrin shock is an infrequent but not rare occurrence. It may be due to (a) anaphylaxis, frequently the result of previous sensitization with a posterior pituitary preparation or to (b) coronary artery constriction with resulting myocardial anoxia, cardiac dilatation and decreased cardiac output. Therapy of shock in the unanesthetized patient should comprise the use of adrenalin or ephedrine, intravenous fluid and oxygen. When it occurs in a patient under ether or cyclopropane anesthesia, adrenalin or ephedrine may prove harmful and, accordingly, only intravenous fluid and oxygen should be employed.—*E.C.H*

Andersen, W. T.

Three cases of hyperthyroidism after weight reducing thyroid treatment. *Acta med. Scandinav.* 104: 589.

The author reports the case histories of 3 women, all past the climacteric stage who had been given large amounts of thyroid for the treatment of obesity. All had severe thyrotoxicosis and auricular fibrillations and 2 of the patients underwent thyroidectomies. The 3rd patient was so ill that operation was not performed. She was given digitalis, quinidine and diiodotyrosine and spontaneous improvement occurred so that operation was not necessary. The condition was thought due to activation of the pituitary by the excessive amount of thyroid.—*J.M.L.*

Baumann, E. J., D. B. Sprinson and D. Marine.

Bromine and the thyroid. *Endocrinology* 28: 793. 1941.

Thyroid administration or excessive thyroid secretion brings about a lowering of blood thyroid probably because of the diuteric and stimulating action of thyroid on the kidney. Hyperplastic thyroid contains more Br than does blood of the same animal while the resting colloid-contaminating gland has no more Br than the blood.—*F. Saunders.*

BROWN, W. E., J. T. BRADBURY AND I. METZGER.

Are the anterior pituitary-like substances gonadotropic? A clinical evaluation in woman. *Am. J. Obst. & Gynec.* 41: 582. 1941.

Twelve cyclic women, subsequently treated with 500 R.U. of chorionic gonadotropin daily for 4 to 6 weeks, received a total of 143 endometrial biopsies before, during and after therapy. Three amenorrheic women were given 500 R.U. of chorionic gonadotropin daily for 6 weeks and endometrial responses were studied weekly for 12 weeks. Seven of the 12 cyclic women treated experienced no alteration in menstrual rhythm. The other 5, however, experienced amenorrhea of 1 to 5 months following therapy. The amenorrhea was associated with a progressive atrophy of the endometrium. Therapy failed to induce bleeding in the 3 amenorrheic patients. It was concluded that chorionic gonadotropins are not gonadotropic in the human female and in sufficient dosage may even be gonadotoxic.—*E.C.H.*

BURGE, E. S., AND H. J. HOLLOWAY.

Clinical experience with pregneninolone. *Am. J. Obst. & Gynec.* 41: 873. 1941.

Pregneninolone was given orally to 28 women with diverse gynecologic and obstetrical complaints related to corpus luteum deficiency. Responses to therapy in patients with menorrhagia, premenstrual tension, menopausal symptoms and nausea of pregnancy were poor. Two of 3 patients treated for threatened abortion aborted. Four patients with secondary amenorrhea treated with 230–300 mg. over intervals of 14 days or less bled after each series of therapy. Endometrial studies indicated that bleeding was of the progestational type. No toxicity was encountered. The authors conclude that pregneninolone in general has not been of clinical value and that it cannot be considered to have properties identical with progesterone.—*E.C.H.*

CATTELL, R. B.

The management of hyperthyroidism complicated by other conditions. *Pennsylvania M. J.* 44: 685. 1941.

In 10 to 12% of patients with hyperthyroidism the syndrome is complicated by other conditions. Many of these aggravate or increase the severity of the hyperthyroidism, and in turn many of these conditions are made more severe by the hyperthyroidism. The management of these cases must be somewhat specialized and directed so as to treat both the hyperthyroidism and the complication. Usually it is best to prepare patients for subtotal thyroidectomy and carry out operation without undue delay. A longer period of preoperative preparation is ordinarily required. Closest cooperation between internist and surgeon is necessary. It should be appreciated that in these cases there is a definitely increased risk, and a higher operative mortality should be anticipated. By conservative preparation and utilization of stage operations, mortality can be kept to a reasonable level, but will still remain approximately 2 or 3 times that for the routine cases of exophthalmic goiter. The relief of hyperthyroidism in these cases frequently results in marked benefit to the associated condition.—*I.B.*

CHU, H. I., S. H. LIU AND T. F. YU.

Water and electrolyte metabolism in diabetes insipidus. *Proc. Soc. Exper. Biol. & Med.* 46: 682. 1941.

In the case studied serum water and electrolyte concentrations were maintained normal by reason of the unlimited water exchange. Water intake restriction or NaCl ingestion produced negative water balance, hemoconcentration, augmented Na and Cl levels in the serum and loss of K from the body. These changes decreased with time despite continued water restriction and NaCl ingestion. Pitressin rapidly restored the water and electrolyte concentrations to normal.—*L. E. Gilson.*

CROWLEY, R. M.

Psychoses with myxedema. *Am. J. Psychiat.* 96: 1105. 1940.

Two more cases of myxedema associated with psychosis are added to the 70 found by the author in the literature. A woman of 38 showed the typical physical signs of myxedema and a paranoid state. Under thyroid therapy she recovered from both with relapses when the treatment was discontinued. A woman of 65 had, associated with myxedema, irascibility, agitation and hallucinations. She improved under thyroid treatment but had a mental relapse (confusion, hallucination, paranoid attitude) leading to a seven-months stay in a mental hospital where she recovered without further thyroid treatment. She remained well for 11 subsequent years without treatment. —*R.G.H.*

FALLS, F. H., V. C. FREDA AND H. H. COHEN.

A skin test for the diagnosis of pregnancy. *Am. J. Obst. & Gynec.* 41: 431. 1941.

The test employes equal parts of colostrum of primiparous pregnant women and sterile saline, each 10 cc. of which contains 1/10 cc. of 1 to 100 merthiolate solution. The mixture is kept refrigerated. An intradermal wheal on the flexor surface of the forearm is produced with 1/50 cc. of the test solution. Tests done upon 265 known pregnant women and 358 non-pregnant controls were thought to indicate the value of this method as an aid in the clinical diagnosis of pregnancy. Ninety-eight per cent of pregnant women gave negative reactions, while 96% of the non-pregnant women yielded characteristic positive reactions. Children were described as reacting similarly to pregnant women.—*E.C.H.*

FAN, C.

Creatine and creatinine metabolism in hypothyroidism. With special reference to the limitations of using creatinine in the urine as a standard of basal energy metabolism. *J. Pediat.* 18: 57. 1941.

The author studied 3 cases of hypothyroidism in Chinese children and noted that the level of blood cholesterol gave a general indication of the therapeutic effect of thyroid, but did not serve as a reliable quantitative indicator of the B.M.R. The degree of creatinuria also did not parallel the level of the basal metabolic rate, either before or after thyroid therapy. The creatinuria was markedly increased on the institution of thyroid therapy but there

was a definite tendency to decrease as this treatment was continued, especially when the patient was on a meat-free diet. The author suggests that creatinuria was the result of decreased capacity of the body tissues to store or utilize creatin and not due to increased production of creatine. The later decrease must be due to the depletion of creatine in the tissue on account of the exaggerated creatinuria during the course of thyroid therapy. The constancy of daily creatinine excretion is only relative and may be influenced by factors other than the thyroid.—*M.B.G.*

GREENE, A. M.

Iodine and cholesterol metabolism in patients with primary myxedema. A clinical and experimental study with a report of results of treatment. *Arch. Int. Med.* 67: 114. 1941.

Nine patients with primary myxedema were studied with reference to behavior of I and cholesterol metabolisms before and after treatment. The cholesterol level of the blood was elevated in all cases of thyroid deficiency. After treatment with thyroid preparations was begun the cholesterol level fell in reciprocal relationship to the rise of the B.M.R. The cholesterol level of the blood was a good criterion of the amount of thyroid substance needed after the beginning of treatment. In a case of compensated myxedema without hypometabolism, thyroxin administered I.V. and desiccated thyroid administered orally exerted no effect on the level of blood cholesterol. The levels of the total blood I and of its organic and inorganic fractions were found to be low or in the low range of normal in 6 of 8 cases of thyroid deficiency. After the administration of small amounts of I the blood-I was elevated, but occasionally this elevation persisted for only a few days. No definite difference was noted in the response of the total I in the blood or of either of its fractions to the administration of inorganic iodine compounds, I in thyroid preparations or organic nonthyroid compounds. The administration of desiccated thyroid to a patient with myxedema produced an I "diuresis" analogous to the diuresis seen in spontaneous hyperthyroidism. This occurred soon after onset of therapy and could not have been produced by induced hyperthyroidism. No absolute correlation could be observed between the variations of the level of I and the level of cholesterol in the blood in myxedema, but there was a tendency for the level of the organic I of the blood to vary inversely with the level of the plasma cholesterol.—*I.B.*

HAMBLEN, E. C.

Some observations on the gynecic employment of equine gonadotropins. *Am. J. Obst. & Gynec.* 41: 495. 1941.

This paper is concerned with a general consideration of the clinical uses and limitations of gonadotropins in gynecic practice. Eight detailed case reports are presented to illustrate general principles in the therapeutic application of gonadotropins in adolescent hypoovarianism, functional uterine bleeding and ovarian sterility. A system of one-two cyclic gonadotropic therapy, which was found effective in selected cases in contrast to an almost negative experience with the use of equine gonadotropin alone, is described: On the 5th to 7th day of the cycle (or upon the conclusion of bleeding) administration of equine gonadotropin is started, 400–800 I.U. being given intramuscularly and daily for 10 days, when chorionic gonadotropic therapy is begun and is given daily in doses of 500 to 750 I.U. for another 10 days. Therapy is discontinued promptly if bleeding occurs before its completion. Rest periods between series of this therapy are advised. The following are some of the conclusions drawn: Adequate gonadotropic therapy may stimulate ovaries which possess normal sensitivity. The pathological ovary salvaged by this therapy is one which is receiving inadequate stimulation from the patient's pituitary. This salvage may be only temporary. Gonadotropic therapy is only one of the methods of treating ovarian failure.—*E.C.H.*

HART, S. C., AND H. B. BREITMAN.

Diabetes insipidus complicating pregnancy. *Am. J. Obst. & Gynec.* 41: 527. 1941.

The report concerns the complication of pregnancy in a 22 year old primipara by diabetes insipidus. Treatment by the nasal insufflation of 50 mg. of posterior pituitary powder 4 times daily was effective. Labor and parturition were normal. Urinary output became normal on 7th postpartum day.—*E.C.H.*

HELLWIG, C. A.

Value of Mallory's aniline blue stain in the histophysiologic diagnosis of goiter. *Arch. Path.* 31: 363. 1941.

This paper is based on the clinical-pathologic study of 50 cases of goiter. As controls, about the same number of normal thyroids from human autopsy material and from animals were stained. It appears that Mallory's aniline blue stain is not a differential stain for toxic colloid. The blue color indicates not a specific chemical alteration of the colloid but only a more liquid and more acid state. Mallory's stain does not help in the histophysiologic study of nodular toxic goiter, in which epithelial proliferation is often absent, and the cellular changes seldom allow one to make a functional diagnosis. The colloid in normal thyroids from fetuses and infants was stained almost exclusively blue.—*Author's summary.*

HOUCKGEEST, A., Q. VAN BRAAM AND J. SANDERS.

Identical twins with simultaneous hypophyseal dwarfism. *Genetica* 22: 261. 1940.

A case history of identical twins with hypophysial dwarfism is described. One twin was successfully treated with a pituitary preparation, 'ambinon-pregnyl.'—*E. W. Lindstrom.*

HOWELL, L. P., D. G. DRIPPS AND H. C. FISHER.

The presence of excessive amounts of gonadotropic principles in the urine of patients with thyroid disease. *Am. J. Obst. & Gynec.* 41: 868. 1941.

The study is based upon gonadotropic assays of 101 urine specimens from 63 patients of both sexes who suffered from various thyroid diseases. The data reported concern 53 patients, 10 climacteric patients being omitted because of physiologic hypergonadotropuria. All 53 patients (22 males and 31 females) excreted amounts of

gonadotropins which varied from 24 R.U. or less per liter of urine to 40 R.U. or more per liter. No explanation is offered for the lack of correlation between type of thyroid disease and the gonadotropic titer or for the fact that some patients with thyroid disease excrete excessive amounts of gonadotropins and others do not.—*E.C.H.*

KAPPES, W. C.

Nodular goiter. *South. M. J.* 34: 517. 1941.

This article is based on 100 cases and a study of the literature. It points out that nodular goiter must be regarded seriously by examiners for employment on account of the threat it represents, over long periods, against the general health and particularly the heart.—*J.C.D.*

KNIES, P. T., AND H. P. LEFEVER.

Metabolic craniopathy: hyperostosis frontalis interna. *Ann. Int. Med.* 14: 1858. 1941.

Medical literature covering 175 years traces the development of present concepts of a clinical syndrome including overgrowth of internal table of frontal bone and at times thickening of diplöe of calvarium. Associated features usually indicate a terminal phase of pituitary hypofunction with attendant endocrine stigmata, particularly obesity, high sugar tolerance, and menopause. Common acromegaloid features suggest earlier phase of pituitary hyperfunction, also indicated by clinical history. Pathogenesis of the bony changes is considered by the authors to precede, often by years, the remainder of syndrome. Five cases are presented demonstrating bony pathology before age 20. Familial predisposition is suggested for the first time by occurrence of hyperostosis in mother and 3 children. General occurrence is 98% in females with associated obesity, virilism and hirsuitism (Morgagni syndrome). Mental changes occur in associated Stewart-Morel syndrome including incompetence, depression, insomnia, nocturnal agitation, memory defect. Advanced cases may show amnesia, hallucinations, ill-defined psychoses. Head injury may initiate bony change or cause discovery of fully developed skull pathology with latent clinical picture. Incompetence, psychoses, and debility constitute social importance in disease diagnosed at average 39 years with 30 years life expectancy. Treatment to date has proved ineffectual. Prevention probably involves correction of juvenile pituitary dysfunction.—*Author's abstract.*

MANSFELD, G.

Humoral ability to transfer chemical heat regulation. *Arch. f. exper. Path. u. Pharmakol.* 196: 573. 1940.

When serum from a dog which has been kept in a hot room is injected into a normal dog a marked decrease in $O_2$ consumption is produced which reaches a maximum 3 to 5 hours after the injection. Absence of the thyroid in the donor abolishes this effect, absence of the hypophysis does not.—*L. E. Gilson.*

MAZER, C., AND E. RAVETZ.

The effect of combined administration of chorionic gonadotropin and the pituitary synergist on the human ovary. *Am. J. Obst. & Gynec.* 41: 474. 1941.

This report deals with a pharmacologic and therapeutic assessment of a mixture of chorionic gonadotropin and Evans' pituitary synergist (Synapoidin, P. D. & Co.). Preoperative therapy of 23 women with this extract (75 to 315 'synergy' U. over 1 to 18 days) resulted in definite stimulation and overstimulation in the ovaries of 20. Therapy of 23 amenorrhea women (5 to 10 injections of 30 'synergy' U. q. 2 days) induced uterine bleeding in 19. Only 2 of the 19, however, continued to bleed after discontinuation of treatment. Treatment of 18 women with functional menometrorrhagia or metrorrhagia (5 to 20 injections of 30 synergy U.) stopped abnormal flowing in 14. Eight women with sterility due to failure of ovulation were treated (5 injections of 15 synergy U. during first half of cycle); 2 conceived promptly.—*E.C.H.*

MOGENSEN, E.

Three cases of Simmonds' Syndrome. *Acta med. Scandinav.* 105: 378. 1940.

A report is given of Simmonds syndrome in two male and one female patient. All 3 cases showed the typical signs of the fully developed syndrome—loss of weight, asthenia, atrophy of the genital organs, changes in hair and skin, premature senility and low B.M.R. In the 2 men some improvement was obtained by treatment with PMS gonadotropin and definite improvement with gonadotropin from PU. In the third patient these substances had no appreciable effect but treatment with estrin caused fair improvement. This patient had severe attacks of spontaneous hypoglycemia which could be controlled by frequent meals rich in carbohydrate.—*J.M.L.*